Original Article

Role of dexmedetomidine in early extubation of the intensive care unit patients

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Abstract

Background and Aims: Patients on ventilatory support in intensive care unit (ICU) require sedation and analgesia to facilitate mechanical ventilation and endotracheal tube tolerance. The selection of the agent should be such that it does not interfere with the early extubation of the patients. We compared the efficacy of dexmedetomidine with midazolam to facilitate extubation of patients from mechanical ventilation in terms of the sedative properties, cardiovascular responses, ventilation, and extubation characteristics and safety profile.

Materials and Methods: A total of 40 adult, mechanically ventilated patients of either sex, aged 18-60 years, meeting the standard criteria for weaning, randomized into 2 groups of 20 patients each, received intravenous infusion of dexmedetomidine (0.2-0.7 mcg/kg/h) or midazolam (0.04-0.2 mg/kg/h) as needed for Ramsay sedation scale 2-4. Extubation following standard extubation protocol was done. Time for extubation and vital parameters were regularly recorded.

Results: The time to extubation in the dexmedetomidine group was significantly lower than in the midazolam group. Heart rate and blood pressure was significantly lower in dexmedetomidine group than the midazolam group at most of the times.

Conclusions: Dexmedetomidine has clinically relevant benefits compared with midazolam in facilitating extubation due to its shorter time to extubation, more hemodynamic stability, easy arousability, and lack of respiratory depression.

Key words: Dexmedetomidine, extubation, intensive care unit, midazolam, sedation

Introduction

The process of weaning from mechanical ventilation is central to the management of critically ill patients. It is a very complex and difficult task. Attention should be paid to wean off the ventilator as quickly as possible after the conditions that warranted placing the patient on the ventilator begin to resolve and stabilize.[1] Delayed or unnecessarily prolonged weaning increases length of intensive care unit (ICU) stay, health-care cost, decreases the ICU bed availability and adversely affects patient outcome.[2,3] Aggressiveness in weaning off the ventilator, however, must be balanced against the possibility that premature discontinuation may occur. Premature discontinuation carries its own set of problems, including difficulty in reestablishing artificial airways and compromised gas exchange, etc.

Majority of ICU patients who are on ventilatory support require intravenous (i.v.) sedative and analgesic medications to facilitate mechanical ventilation, improve tolerance to the endotracheal tube, the invasive procedures, physiotherapy, tracheal suctioning, turning postures, changing of dressings, allays anxiety, blunts excessive hemodynamic, and metabolic responses.[4-6]

Two major classes of medications used for this purpose in ICU are the sedative hypnotic agents and opioid analgesics. Benzodiazepines are the agents most commonly used to provide sedation in ICU.[7,8] Lorazepam given by intermittent boluses or continuous i.v. infusion was recommended in the Society of Critical Care Medicine, 2002 consensus guidelines, as the preferred sedative drug for ICU patients

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who require prolonged mechanical ventilation. Whereas, midazolam was recommended only for short term (<48 h) sedation because of concerns for unpredictable awakening observed after prolonged infusion.[9] Midazolam causes a fall in systemic vascular resistance that is more evident when vascular resistance is raised, such as in hypertensive patients.[10] It produces some respiratory depression and also apnea when given along with opioids. Its elimination is prolonged in critically ill patients resulting in prolongation of its actions and extubation failure.[11-13]

The α_2 agonist dexmedetomidine is a newer sedative and analgesic agent used for ICU sedation for up to 24 h after surgery.[14,15] It provides a hemodynamic stability[14,16,17] and appears to have no clinically important adverse effects on respiration.[18-20] 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.[14,21] It does not affect the respiratory drive and therefore, it should not interfere with weaning from mechanical ventilation.[22]

In this study, we compared the efficacy of dexmedetomidine with midazolam to facilitate extubation of patients from mechanical ventilation in terms of the sedative properties, cardiovascular responses, ventilation, and extubation characteristics and safety profile.

Materials and Methods

This study was conducted in a randomized, open labeled manner on 40 adults, aged 18-60 years. All these patients were postabdominal surgery patients, being mechanically ventilated for <96 h prior to start of study drug infusion, and were anticipated to be weaned-off mechanical ventilation in next 24 h. A written informed consent was taken from legally acceptable relatives of all patients. Patients with significant liver (Childs Pugh class-C) or kidney disease, severe neurological disorders, acute myocardial infarction, heart block, heart rate <50 beats/min, systolic blood pressure <90 mm Hg despite continuous infusions of vasopressors, receiving other sedatives and anticonvulsant drugs, pregnant/lactating females, and patients allergic to midazolam or dexmedetomidine were excluded from the study.

As institutional protocol, these patients were receiving morphine or fentanyl for analgesia and midazolam or lorazepam, for sedation as per choice of treating intensivist. Readiness for weaning trial was considered on the basis of following criteria; awake, adequate cough on suctioning, PaO_2 >60 mm Hg, oxygen saturation ≥90%, fraction of inspired oxygen ≤0.4, positive end expiratory pressure ≤10 cm H_2O, respiratory rate (RR) ≤35/min, ventilation ≤15 L/min, no inotropic or vasopressor infusions, mean arterial pressure >60 mm Hg, and no evidence of acute myocardial ischemia (i.e., chest pain, consistent electrocardiogram findings, elevated biomarker levels, or new arrhythmia). To check the readiness for weaning all these patients were subjected to daily sedation interruptions and were assessed hourly for wakefulness, defined as Ramsay sedation scale (RSS) score 1-4 and ability to perform at least 3 of the following on request: Eye opening, tracking, hand squeezing, and toe movement. Patients were subjected to a spontaneous breathing trial (SBT). Patients who successfully completed a 2 h trial of spontaneous breathing were further tried for discontinuation of mechanical ventilation and possible extubation depending upon their ability to maintain and protect airway and their ability to cough and clear secretions. On the other hand, SBT was discontinued if there was tachypnea (RR >35/min for 5 min), hypoxia (SpO_2 < 90%), sustained changes in heart rate and blood pressure of more than ±20% or increased anxiety and diaphoresis. The patients who failed SBT were randomized into two groups of 20 patients each to receive either of the study drug infusion protocol using computer-generated random numbers.

Group I: Patients received i.v. infusion of dexmedetomidine at a rate of 0.2-0.7 mcg/kg/h (adjusted as needed for the desired level of sedation i.e., RSS 2-4).

Group II: Patient received i.v. infusion of midazolam at the rate of 0.04-0.2 mg/kg/h (adjusted as needed for the desired level of sedation i.e., RSS 2-4).

Sedation was categorized into three levels according to RSS as:

1. Insufficient: If sedation level was Grade 1 on the RSS.
2. Adequate (desired): If sedation level was Grade 2-4 on the RSS.
3. Excessive: If sedation level was Grade 5-6 on the RSS.

After starting weaning, the analgesia was provided with regular paracetamol infusion to all patients. The study drug infusion was given up to a maximum period of 24 h. Hemodynamic parameters were recorded every 4 hourly during study drug infusion and then every 2 hourly after discontinuation of study drug. The patients were regularly accessed for possible extubation. After meeting the criteria for extubation, the extubation was done following standard extubation protocol and the time for extubation (from start of the study drug infusion until extubation) and duration of study drug infusion given was recorded.

Patients who maintained effective spontaneous breathing without any mechanical assistance for 24 h after extubation were considered as successfully weaned and those who did not, were excluded from the study and were considered as extubation failure. The arterial blood gas sample was taken at the beginning of weaning, just before extubation and 1 h after extubation.

Statistical analysis

Quantitative data were described in mean ± standard deviation and were compared using Students's *t* test or Mann-Whitney test. Categorical data were described by absolute and percentage frequencies and were compared using Chi-square test. Differences were considered significant when $P \leq 0.05$.

Results

Patients in the two groups were comparable demographically in terms of age, sex, body mass index, indication for putting on the ventilator, and duration of ventilation prior to start of study drug infusion [Table 1].

Table 1: Demographic profile

Group	Group I	Group II	*P* value
	Dexmedetomidine	Midazolam	
Age (years)	43.35±11.595	39.00±14.127	0.294
Sex (male/female)	12/8	13/7	0.744
BMI (kg/m^2)	25.778±3.725	25.911±3.082	0.665
Ventilator indication			
Poly-trauma	8 (40%)	7 (35%)	
Sepsis	6 (30%)	8 (40%)	
Prolonged abdominal surgery	6 (30%)	5 (25%)	
Period of ventilation prior to starting study drug infusion	92 h, 36 min	94 h, 15 min	

BMI = Body mass index

The level of sedation as assessed by RSS among patients in two groups was comparable at various time intervals [Table 2]. Most of patients in both groups remained adequately sedated throughout the study period. Excessive sedation was seen only in midazolam group (two patients at 12 h, two patients at 16 h and one patient at 20 h). No case of excessive sedation was seen in dexmedetomidine group.

The time to extubation was found to be significantly lesser in the dexmedetomidine group (24.210 ± 1.6651 h) than in the midazolam group (31.350 ± 3.3447 h) [Table 3].

Patients in both groups remained hemodynamically stable throughout the study period. The difference in heart rates in the two groups was comparable and was statistically insignificant at 0-12 h. Whereas, the heart rates in the dexmedetomidine group were significantly lower than in the midazolam group at 16, 20, and 24 h after the drug infusion. In the intragroup comparison, the mean fall in heart rates from the baseline values was significant in dexmedetomidine group at 16, 20, and 24 h, whereas it was insignificant in midazolam group. After extubation the heart rate in the dexmedetomidine group was found to be significantly lower than in the midazolam group, when the two groups were compared with each other from the time of extubation until 12 h postextubation [Table 4 and Figure 1].

The baseline values of systolic blood pressure in the dexmedetomidine group and midazolam group were statistically insignificant. The change in mean systolic blood pressure from baseline value until 16 h of starting the study drug infusion was statistically insignificant in both groups. However, a significant fall from baseline was observed at 20 h in dexmedetomidine group alone and at 24 h in both dexmedetomidine and midazolam groups. On intergroup comparison, the fall in systolic blood pressure was comparable in both groups except at 24 h where a statistically significant fall in systolic blood pressure was observed in dexmedetomidine group as compared with midazolam group. Significantly lower systolic blood pressure values in dexmedetomidine group were observed as compared to midazolam group at various time intervals after

Table 2: Adequacy of sedation

Time (h)	Group I			Group II			*P* value
	Dexmedetomidine			Midazolam			
	Inadequate sedation	Adequate sedation	Excessive sedation	Inadequate sedation	Adequate sedation	Excessive sedation	
0	20	0	0	20	0	0	1.000
4	2	18	0	4	16	0	0.382
8	1	19	0	3	17	0	0.298
12	0	20	0	2	16	2	1.000
16	0	20	0	0	18	2	0.152
20	1	19	0	1	18	1	0.799
24	0	20	0	0	20	0	1.000

extubation also. The comparative diastolic blood pressure trends at various time intervals before and after extubation were almost similar as that of systolic blood pressure in both dexmedetomidine and midazolam groups [Figure 1].

The baseline values of oxygen saturation (SpO_2) in the dexmedetomidine group and midazolam group were statistically insignificant. On intergroup comparison, the oxygen saturation values were comparable in both groups except at 24 h after starting the study drug infusion, where significantly lower value of SpO_2 was observed in midazolam group as compared to dexmedetomidine group. After extubation, the oxygen saturation in the dexmedetomidine group was found to be significantly higher than in the midazolam group at all-time intervals, when the two groups were compared with each other statistically [Figure 2].

Discussion

The ideal drug for sedation in the ICU is one with a rapid onset of action, a short duration of action and which produces sedation without affecting the cardiovascular or respiratory system. It should have a short elimination half-life with no accumulation on repeated or continuous administration,[23] and should be metabolized by pathway not dependent on renal, hepatic, or pulmonary functions. Etomidate, opioids, benzodiazepines, thiopentone, and ketamine are few examples which individually lacked some of these desirable properties and hence failed to become the drug of choice.[24,25]

In daily practice of intensive care, the trend has been to use a combination of opioids and benzodiazepines. Opioids in the usual dose are excellent sedatives, analgesics, producing euphoria, and drowsiness with little effect on arterial blood pressure. However, opiates by themselves are not appropriate for prolonged, continuous sedation because of the number of side-effects such as decreased intestinal motility, tolerance, withdrawal after discontinuation of drug, and possible influence on immune status.[26,27]

Benzodiazepines such as diazepam or lorazepam act rapidly, but the presence of active metabolites prolongs recovery.

Table 3: Time to extubation (in h)

Group	Mean ± SD	*P* value
Dexmedetomidine	24.210±1.6651	0.0260
Midazolam	31.350±3.3447	

SD = Standard deviation

Table 4: Heart rate trends before and after extubation

Time	Dexmedetomidine group	Midazolam group	*P* value
Before extubation			
0 h	117.44±11.703	117.00±6.440	0.683
4 h	112.44±9.954	113.70±6.199	0.497
8 h	110.50±12.557	110.95±6.048	0.796
12 h	103.83±11.719	111.50±5.568	0.113
16 h	95.33±13.408	109.50±5.568	0.012
20 h	91.22±12.670	110.7±5.992	0.020
24 h	86.60±12.331	109.05±6.452	0.024
After extubation			
0 h	105.15±14.295	118.25±6.290	0.020
2 h	95.70±12.503	114.60±7.315	0.017
4 h	91.65±12.368	110.60±7.432	0.041
6 h	88.30±11.970	107.00±4.377	0.031
8 h	86.25±11.652	107.70±6.097	0.020
10 h	85.40±11.348	108.00±5.026	0.036
12 h	84.85±9.949	108.95±5.671	0.024

n = 20, values are given as mean heart rate (beats/min) ±SD. SD = Standard deviation

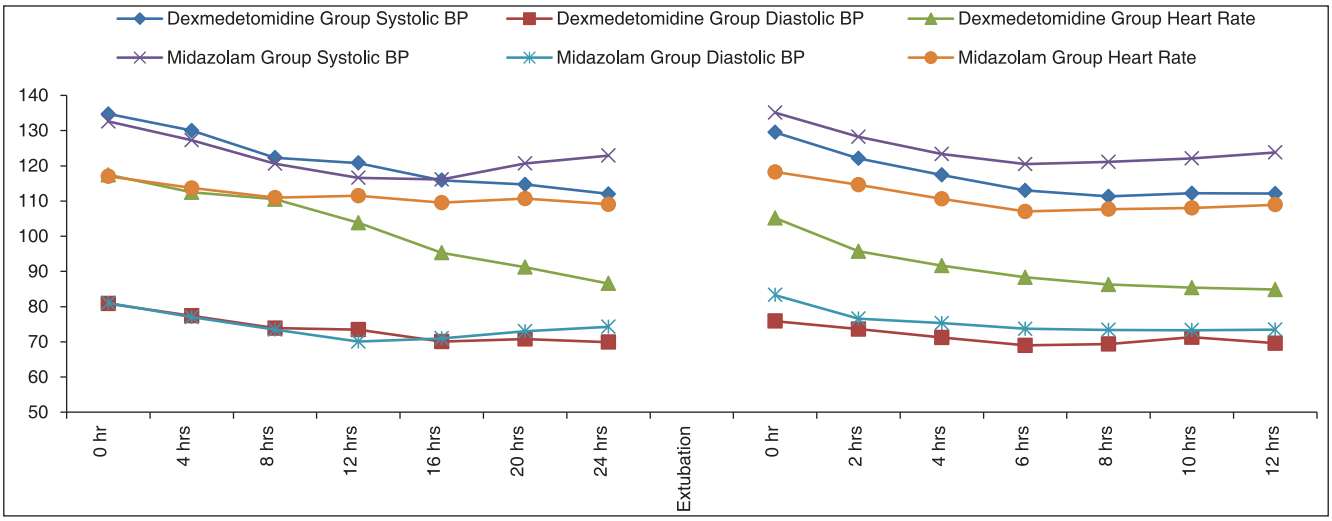

Figure 1: Hemodynamic trends

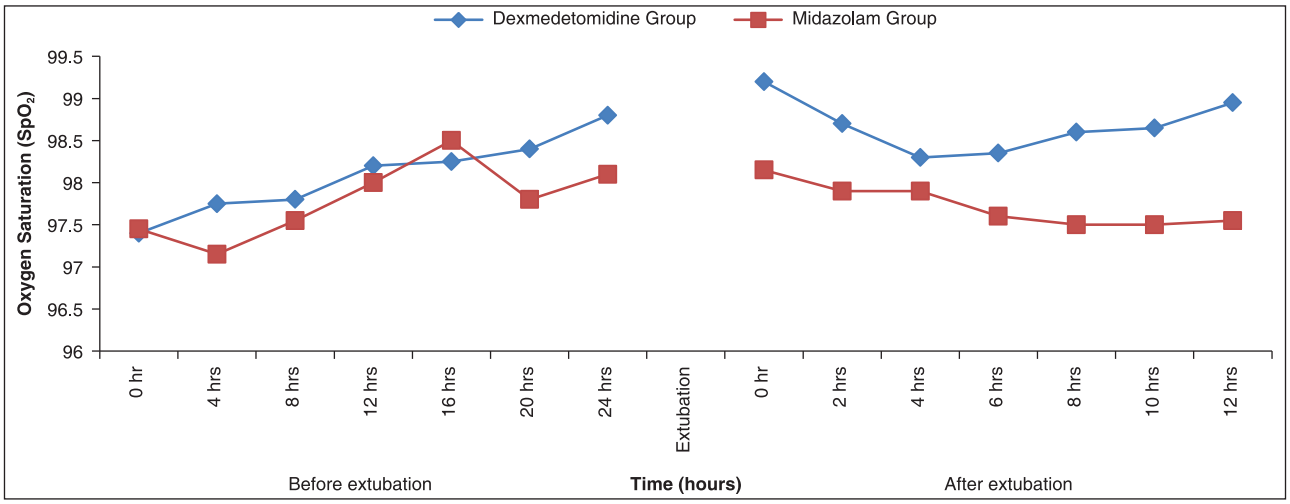

Figure 2: Oxygen saturation (SpO_2) trends

Midazolam a water-soluble benzodiazepine with sedative, anxiolytic, anticonvulsant and muscle relaxant properties, with low toxicity[19] has been used as a sedative in ICU, but it produces respiratory depression, delayed recovery and hypotension.[6] A "midazolam infusion syndrome" resulting from high doses, is characterized by delayed arousal after discontinuation, leading to an increase in the length of ventilatory support.[28]

Dexmedetomidine a new, potent alpha-2 agonist acting in the locus ceruleus, inhibits sympathetic stimulation, and provides analgesia and sedation without respiratory depression and hemodynamic instability. It produces only mild cognitive impairment allowing easy communication between health-care provider and the patient in ICU.[14-20]

In the present study, we compared the efficacy of dexmedetomidine and midazolam in facilitating extubation in patients on mechanical ventilatory support. Following the start of dexmedetomidine infusion, there was no difference in the percentage of time within the target RSS range (96.6% in dexmedetomidine group vs. 87.6% in midazolam group ($P > 0.05$). There were 3.3% and 8.3% patients who were inadequately sedated in dexmedetomidine and midazolam group respectively. There were 4.2% patients over-sedated midazolam group and none in dexmedetomidine. Our study is in accordance with that of Riker *et al.*, who reported that there was no difference in the primary efficacy outcome in terms of percentage of time within the target Richmond agitation sedation scale (RASS) range (77.3% for dexmedetomidine - treated patients and 75.1% for midazolam - treated patients; difference, 2.2% [95% confidence interval (CI), −3.2-7.5%]; $P = 0.18$).[29] The MIDEX trial comparing midazolam with dexmedetomidine with respect to the proportion of time at target sedation level (measured by RASS) in ICUs of 44 centers in nine European countries concluded that dexmedetomidine/midazolam ratio in time at target sedation was 1.07 (95% CI, 0.97-1.18).[30]

In our study, the time to extubation in the dexmedetomidine group (24.210 ± 1.6651 h) was found to be significantly lower (7.14 h) than in the midazolam group (31.350 ± 3.3447 h). Venn *et al.*[18] in 2000 compared dexmedetomidine with propofol for sedation in the ICU. They showed that the extubation times were similar and rapid with the use of both sedative agents (median [range] 28 [20-50] and 29 [15-50] min [$P = 0.63$] for the propofol and dexmedetomidine groups, respectively). Shehabi *et al.* in 2004 showed that mean time to extubation was shorter in dexmedetomidine group (24.21 h [22-28 h]) than midazolam group (31.35 h [26-38 h] [$P < 0.05$]).[31]

Despite the similar levels of target sedation achieved by patients treated with dexmedetomidine and midazolam, several important differences were noted. Mean systolic blood pressure decreased by 17% in dexmedetomidine group and 5% in midazolam group ($P < 0.05$), whereas the mean diastolic blood pressure was reduced by 13.97% in dexmedetomidine group and 9.26% in midazolam group ($P < 0.05$). In preextubation period, the mean heart rate remained lower in dexmedetomidine group than midazolam group at all times, but it was statistically significant at 16th, 20th, and 24th h of starting the infusion. In postextubation period, the heart rate was significantly lower in dexmedetomidine group as compared with midazolam group. A 28% reduction in heart rate from baseline was seen in dexmedetomidine group, whereas it was 7% reduction midazolam group ($P < 0.05$).

Venn *et al.*[18] also reported significantly lower heart rate in the dexmedetomidine group (mean [standard deviation] 75 [6]

vs. 90 [4] beats/min) however, no significant differences were found in arterial pressures between the groups. Shehabi *et al*. in 2004 also reported a 16% reduction in mean systolic blood pressure and 21% reduction in heart rate over the first 4 h followed by minimal (±10%) changes throughout the infusion.[31] In 2008, Arpino *et al*.[32] also found that the heart rate trended down after dexmedetomidine initiation in most patients, but did not result in the discontinuation of dexmedetomidine in any patient. The addition of dexmedetomidine was associated with minimal changes in mean arterial pressure.

In our study, the mean SpO_2 levels in postextubation period remained significantly higher in dexmedetomidine group (98.7%) as compared with midazolam group (97.7%). Patients sedated with dexmedetomidine were easily arousable and cooperative with the procedures such as physiotherapy, radiology, suctioning, positioning, etc., without showing irritation. Dexmedetomidine treated patients showed rapid recovery in the level of consciousness after discontinuation of drug infusion as compared to midazolam where 10% of patients were over-sedated. All patients were successfully extubated without any weaning failure.

Though the baseline sedation score following daily sedation interruption in both groups were comparable, but still the midazolam infusion given prior to start of study drug infusion could also have resulted in delayed time to extubation in midazolam group. Other limitations of study are a small sample size and we also did not compare the severity of sickness and types, duration and severity of surgery in two groups. Future studies of ICU sedation must look beyond the quality of sedation to focus on additional important clinical outcomes like delirium and long-term cognitive functions, etc.

We hereby conclude that dexmedetomidine has clinically relevant benefits compared to midazolam in facilitating extubation because of its shorter time to extubation, more hemodynamic stability, easy arousability and lack of respiratory depression; hence, it can be used as an effective, and safe sedative agent to facilitate extubation in ICUs.

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