Original Research Article

Indian Journal of Anesthesia and Analgesia
2018;5(1):013-021
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.5118.3

Comparative Study of Dexmedetomidine vs Midazolam Infusion for ICU Sedation

Akhilesh Kumar Singh[1], Amarjeet Kumar[2], Lakshmi Sinha[3], Chandni Sinha[4], Vijay Kumar Gupta[5]

[1,2]Senior Resident [4]Associate Professor, Department of Anaesthesia [3]Senior Resident, Department of General Surgery, All India Institute of Medical Sciences, Patna, Bihar 801507, India. [5]Professor & Head, Department of Anaesthesia, Patna Medical College and Hospital, Patna, Bihar 800004, India.

Abstract

Introduction: Sedation & Analgesia are generally taken as one entity in intensive care unit and disproportionate use of sedative is associated with adverse outcomes including patients restlessness, excessive sedation, longer ICU (intensive care unit) and hospital stay, an increased incidence of ventilator-associated pneumonia and greater hospital costs. Pain was considered as the 1st cause of inadequate analgesia/sedation. Dexmedetomidine possesses anxiolytic, hypnotic, analgesic and easy arousability properties. *Aim of the study:* was to Compare the effectiveness of sedation with Dexmedetomidine and midazolam in Critically ill patients admitted in ICU and their haemodynamic and respiratory parameter. *Methods:* The patients were randomly divided into two groups, 20 in each group. Group A receive loading dose of dexmedetomidine 1µg/kg body weight over 10 minutes followed by 0.2 to 0.7 µg/kg/hr of maintenance infusion dose. Group B receive Intravenous midazolam with loading dose of 0.05 mg/kg body weight; followed by 0.05 to 0.1 mg/kg/hr of maintenance dose. Analgesia with tramadol bolus doses 1 to 2 mg/kg body weight was given as per need. *Observation:* Heart rate (HR), Mean arterial pressure (MAP), Oxygen saturation (SPO_2), Respiratory rate (RR), Quality of sedation using Ramsay sedation score (RSS). *Result:* The mean total sedation requirement was 495±185 µg in dexmedetomidine group and 55.7±21.7 mg in midazolam group. The mean hourly dose of sedative was 0.34±0.13 µg/kg/hr in dexmedetomidine group and 0.042±0.017 mg/kg/hr in midazolam group. *Conclusion:* Dexmedetomidine provide more acceptable sedation compared to midazolam. Patients remained hemodynamically stable in Dexmedetomidine group when compared to midazolam group.

Keywords: Dexmedetomidine; Midazolam; ICU; Sedation.

Introduction

Critically ill patients in the intensive care unit subjected to many adverse clinical situations because of their coexisting disease or the ICU environment that produce harmful psychological and physiological changes. These changes are due to increased levels of catecholamines and other stress hormones. The critically ill patients in the ICU are subjected to pain and discomfort due to endotracheal intubation and mechanical ventilation, intermittent physiotherapy, tracheal suction etc. Nursing procedures can also be unpleasant for them [1]. The noise level produced by the monitoring and support equipments are usually high and irritating and the lighting in the ICU surroundings are not pleasant rather it is unsoothing to the eyes, enhancing the adverse reactions [2].

Sedation and analgesia are generally taken as one entity in intensive care unit and disproportionate use of sedative is associated with adverse outcomes including patients restlessness, excessive sedation, longer ICU and hospital stay, an increased incidence of ventilator-associated pneumonia and greater hospital costs.

An ideal sedative should provide a rapid onset and a rapid recovery, having sedative, analgesic, amnesic property, easily titratable, without any

Corresponding Author: Amarjeet Kumar, Senior Resident, Department of Anaesthesia, All India Institute of Medical Sciences, Patna, Bihar 801507, India.
E-mail: amarjeetdmch@gmail.com

Received on 08.10.2017, **Accepted on** 23.10.2017

haemodynamic disturbances, no any respiratory depression and devoid of withdrawal effects [3].

Dexmedetomidine, a unique sedative agent, alfa-2 adrenergic agonist, provides proper sedation with easy arousability and has also analgesic effect. It does not have a respiratory depressive action. It is now established as a novel approach to intensive care sedation and has the potential to reshape patient care in the ICU [4].

Aim of the Study

Aim of this study was to evaluate the sedation characteristics of dexmedetomidine and midazolam in postoperative mechanically ventilated patients in our ICU.

Methods

This prospective randomized double blinded study was done in P.M.C.H, Patna. Forty adult Patients (ages 18 to 60 years), between ASA grade I to III, who were intubated and expected to be mechanically ventilated for a period of approximately twenty four hours were included in the study. After approval by hospital ethical committee, informed consent was obtained from one of patient's close relatives. The patients were randomly divided into two groups, 20 in each group.

Group A: Received a loading dose of dexmedetomidine 1µg/kg body weight over 10 minutes followed by 0.5 µg/kg/hr of maintenance infusion dose.

Group B: Received a loading dose midazolam 0.05 mg/kg body weight; followed by 0.06 mg/kg/hr of maintenance infusion dose.

Exclusion Criteria

Known or suspected allergy to Dexmedetomidine or midazolam, Severe hepatic or renal disease, Requirement of muscle relaxants except for intubation (succinylcholine), Pregnancy or lactation, Severe pulmonary or cardiac disorder. Analgesia with tramadol bolus doses 1 mg/kg body weight was administered as per need. Throughout the study, the efficacy of sedation was assessed by using the Ramsay sedation score. Three levels of sedation were considered : (1) Adequate, when the sedation level was grade 2,3,4 or 5 on Ramsay scale (2) Insufficient when the sedation level was grade 1 and (3) Excessive, when the sedation level was grade 6 on Ramsay scale. The aim of our study was to achieve a target sedation of grade 3 on Ramsay scale for most of the sedation hours and with no pain at rest and minimal pain at movement. Whenever the sedation was not considered adequate, the rate of continuous infusion of the sedative was increased or decreased by 10% at a time and efficacy of sedation was reassessed 15 minutes later. Pain was considered as the 1st cause of inadequate analgesia/ sedation and was treated first with low dose of tramadol before further increasing the dose of Dexmedetomidine or midazolam.

All the patients were mechanically ventilated and the ventilatory parameters were adjusted so as to maintain normocapnia and a partial pressure of oxygen in arterial blood (PaO_2) between 75 to 100 mmHg. At the end of each shift, the nurse attending the patient was interviewed regarding the efficacy and overall quality of sedation. In patients considered fit for weaning from mechanical ventilation, weaning was started while the patients were still sedated. The infusion of dexmedetomidine or midazolam was discontinued when clinical assessment showed that sedation was no longer required, or when a maximum period of 24 hours was reached, to allow assessment of post sedation responsiveness. When sedation was required thereafter, the usual regimen of our ICU was followed. Post sedation responsiveness was assessed after stoppage of sedation, until the patient could obey simple but specific command. The following parameters were monitored during the study: Quality of sedation using Ramsay sedation score (RSS), electrocardiogram (ECG), heart rate (HR), means blood pressure (MAP), central venous pressure(CVP), Oxygen saturation (SPO2), and adverse effects

Statistical Analysis

Data were expressed as mean ±SD. Group means were compared using student's t-test. A 'P' value of <0.05 was considered statistically significant.

Observations

Forty patients were entered into this study. Twenty patients were in dexmedetomidine group and twenty in midazolam group. Demographic data shown in Table 1.

The mean age in dexmedetomidine groups was 40.1±15.46 yrs and that in midazolam group was 41.1±21.36 yrs (p=0.8662). The mean weight was

53.15±6.60 and 54.65±6.11kg respectively (p=02387). The male to female ratio was 13:7 in dexmedetomidine group and 14:6 in midazolam group. There was no difference between the two groups with regards to age, weight, sex and ASA grades. The patient population in both the groups were also similar with regards to the type of surgery done.

The mean total sedation requirement was 495±185 µg in dexmedetomidine group and 55.7±21.7 mg in midazolam group. The mean hourly dose of sedative was 0.34±0.13 µg/kg/hr in dexmedetomidine group and 0.042±0.017 mg/kg/hr in midazolam group shown in Table 2.

Patients in midazolam group required more number of boluses of analgesics compared to dexmedetomidine group as shown in Table 3.

Heart Rate

The mean heart rate at the start of infusion was 118.25±31.93 bpm in dexmedetomidine group and 116.5±31.38 in midazolam group (P=0.862). Following the start of infusion heart rate was lowered in both the groups. The lowest heart rate in both groups was observed at 24 hrs of infusion. At the end of 24 hour, the heart rate in dexmedetomidine group was 95.35±51.72 and that in midazolam group was 106.5±52.28 (P=0.501) .The heart rate was lowered to a greater extent in dexmedetomidine group than in midazolam group at the end of 24 hour of infusion. This was however statistically not significant as shown in Figure 1.

The baseline MAP (mmHg) in the dexmedetomidine and midazolam Group were 105.95±6.58 and 106.2±11.50 mmHg respectively (P=0.933). Patient in dexmedetomidine group had a mean MAP of 102.65±6.40 mmHg compared to101.2+12.85 observed in the Midazolam group at 10 min from start of infusion(P=0.654). At one hour from start of infusion, the corresponding values were 100.65±6.53 and 103.2 ±13.95 mmHg in dexmedetomidine group and midazolam group respectively (P=0.463). The maximum fall in MAP in dexmedetomidine group was from baseline values of 105.95±6.58 mmHg to 97.45±6.80 mmHg at 8 hours from start of infusion. The maximum fall in midazolam group was from baseline values of 106.2±11.50 mmHg to 100.2mmHg at 12 hours of infusion. Throughtout the period of study, patients in dexmedetomidine group maintained a lower MAP than patients in midazolam group at corresponding times .The fall of MAP in both the groups over the period of study was found to be statistically significant at all time points from the baseline values, in both the groups as shown in Figure 2.

The baseline CVP in the dexmedetomidine and midazolam Groups were 11.25±1.51 and 9.9±2.03

Table 1: Showing demographic characteristics of study population

Parameters	Dexmedetomidine (N=20)	Midazolam (N=20)	P Value
Age	40.1 ± 15.46	41.1 ± 21.36	0.8662
Weight	53.15 ± 6.60	55.65 ± 6.61	0.2387
ASA grades I/II	8/9/3	11/7/2	
Male : Female	13:7 (65/35%)	14:6 (70/30%)	
Type of surgery	Gen. Surgery		

Table 2: Showing sedative requirements in both the group

Parameters	Dexmedetomidine (n=20)	Midazolam (n=20)
Total dose of sedative in 24 hour	495±185 µg	55.7±21.7 mg
Hourly dose of sedative	0.34±0.13 µg/kg/hr	0.042±0.017 mg/kg/hr
No. of patients in whom the rate of infusion had to be changed in 24 hour		
< 2 times	2	0
2 – 5 times	9	11
≥ 6 times	9	9

Table 3: Showing analgesic requirements in both the groups

Parameters	Dexmedetomidine(n=20)	Midazolam(n=20)
Number of patients who needed bolus dose of analgesics		
≤ 3 times	14	10
≥ 4times	6	10
Total no. Of boluses used	58	69

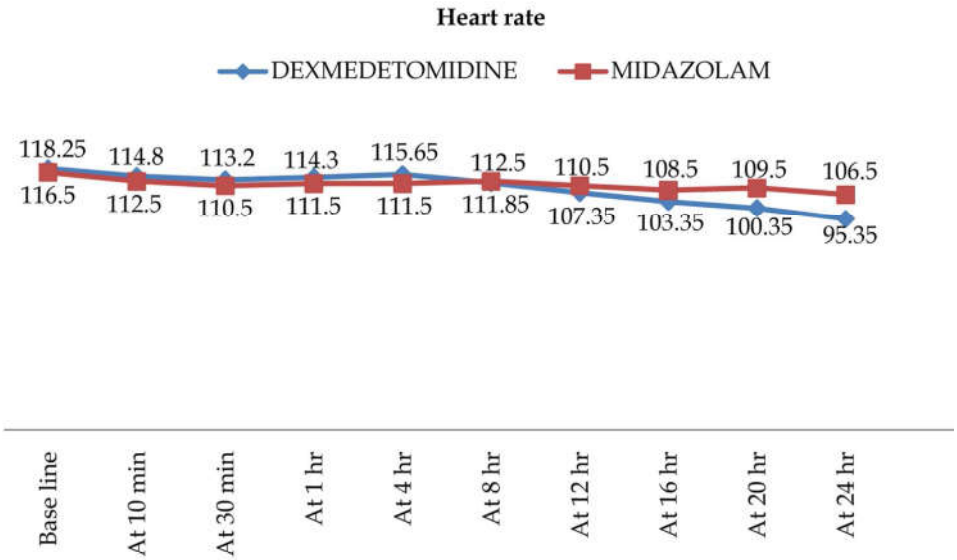


Fig. 1: Line Graph showing HR in Dexmedetomidine and midazolam group

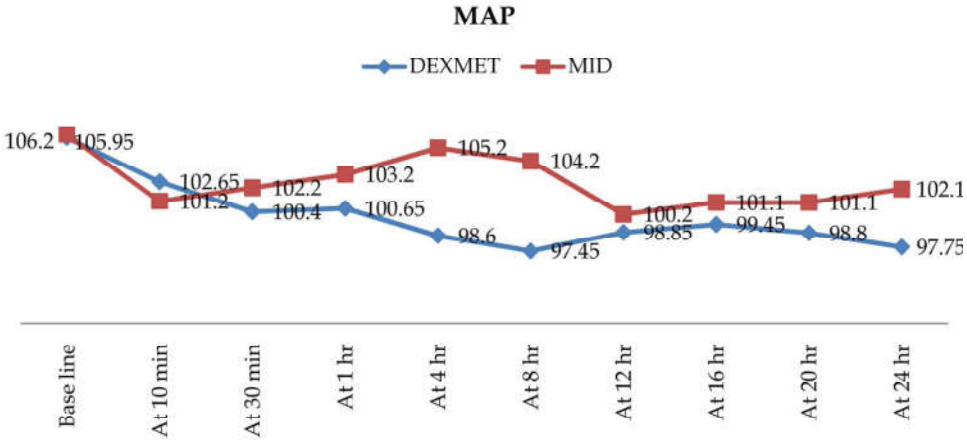
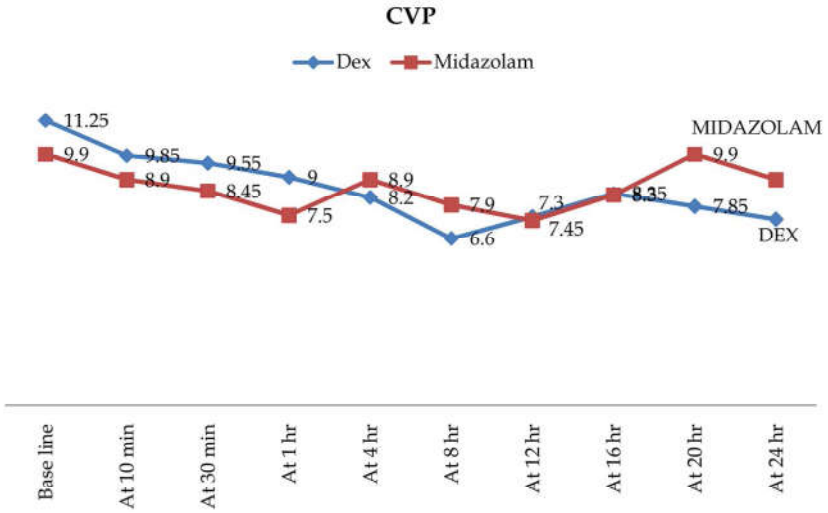


Figure 2: Line Graph showing mean arterial Blood Pressure (mmHg) in Dexmedetomidine and Midazolam Group



Central Venous Pressure

Fig. 3: Line Graph showing CVP in Dexmedetomidine and midazolam group

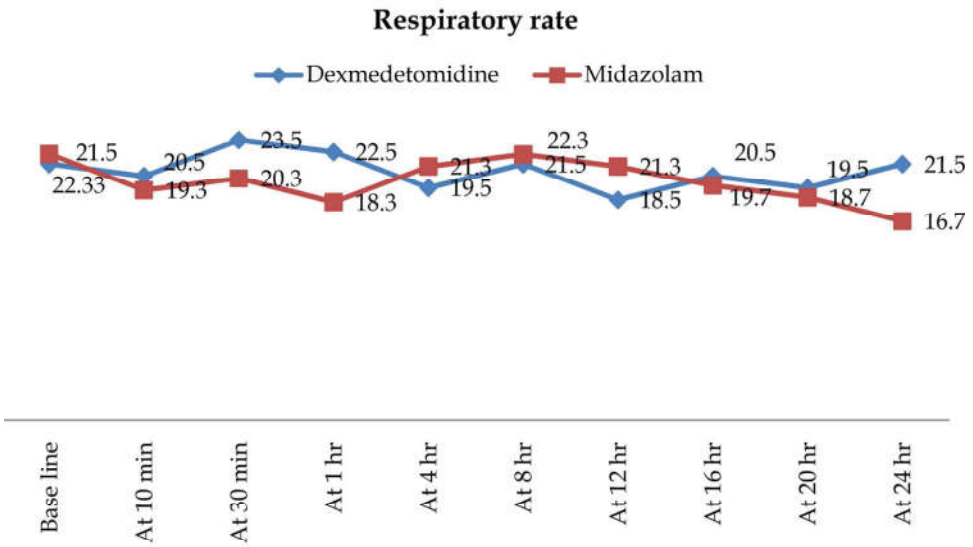


Fig. 4: Line chart showing Respiratory Rate (per minute) in the Dexmedetomidine and Midazolam group

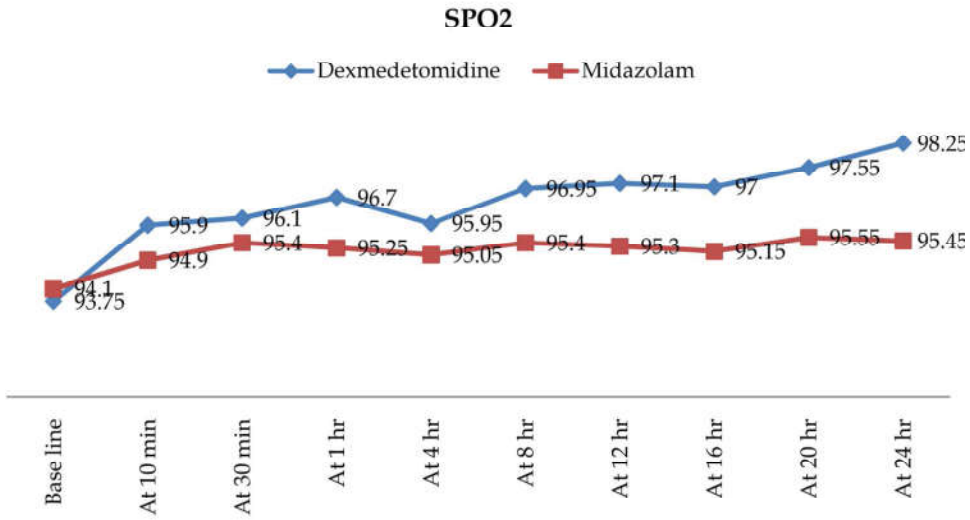


Fig. 5: Line graph showing SpO2 (%)

mmHg respectively(P=0.022). In both the groups there was a significant fall in CVP with time. The lowest value of CVP was recorded at 8 hours of infusion in dexmedetomidine group and at 12 hours in midazolam group. The fall of CVP in dexmedetomidine group over the period of study was found to be statistically significant at all time points from the baseline values. The fall in CVP from baseline value in midazolam group was statistically significant at 30 minutes, 1 hour, 8 hours, 12 hours and 16 hours as shown in Figure 3.

Respiratory Rate

The mean baseline spontaneous respiratory rate at the start of infusion was 21.5 breaths per minute in dexmedetomidine group and 22.33 breaths per minute in midazolam group. At the end of study, the respiratory rate in dexmedetomidine group was 21.5 breaths per minute compared to 16.7 breaths per minute in midazolam group. There was minimal change in RR in dexmedetomidine group while in midazolam group changes were greater as shown in Figure 4.

SpO_2

All the patients in both groups maintained a percentage saturation of oxygen around 95% while on spontaneous breathing throughout the study shown

Table 4: Ramsay sedation score with time

Time period	Dexmedetomidine			Midazolam		
	Agitated (RSS=1)	Adequate (RSS=2-5)	Excessive (RSS=6)	Agitated (RSS=1)	Adequate (RSS=2-5)	Excessive(RSS=6)
Base line	8	12	0	6	14	0
1 hr	1	19	0	3	17	0
4 hr	0	20	0	2	18	0
8 hr	0	20	0	1	18	1
12 hr	0	19	1	0	18	2
16 hr	0	20	0	1	17	2
20 hr	0	19	1	0	18	2
24 hr	0	20	0	0	20	0

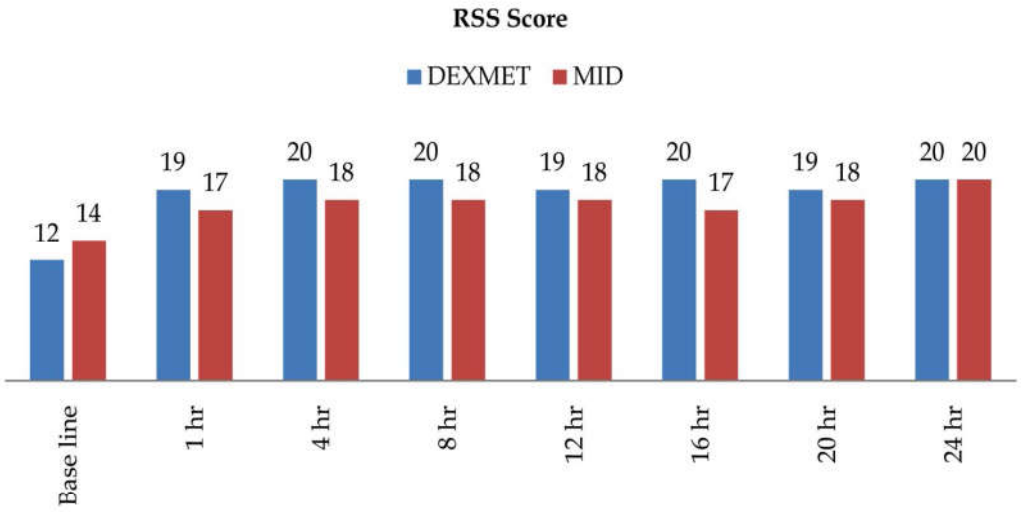


Fig. 6: Acceptable:Ramsay sedation score 2-5

in Figure 5. Respiratory rate (in minutes) is maintained in both Dexmedetomidine and Midazolam Group. The change in respiratory rate was similar in both the groups and was not found to be statistically significant

Quality of Sedation

We compared the quality of sedation using Ramsay sedation score. At the start of the study 8 patients in dexmedetomidine group and 6 patients in midazolam group were agitated (RSS=1). By 1 hour from start of sedation the numbers had decreased to 1 in dexmedetomidine where as 3 patients in midazolam group were still agitated. Eighteen patients in the dexmedetomidine group had a baseline Ramsay sedation score of less than optimal (RSS=3), compared to 16 patients in midazolam group. By the end of 1 hour from start of infusion, 9 patients in dexmedetomidine group had achieved the sedation score of 3 in contrast to only 5 patients in midazolam group as shown in Table 4.

While comparing the incidence of inadequate and excessive sedation in both the groups, we observed a similar trend in inadequate sedation in both the groups. However the patients in dexmedetomidine group remained in excessive sedation on considerably fewer occasions compared to patients in midazolam group. This was considered statistically significant. The patients in midazolam group needed more frequent changes in their infusion rate than patients in dexmedetomidine group.

A total of 480 observations about the quality of sedation was made in both groups. Patients in dexmedetomidine group achieved a target Ramsay score of 3 on statistically more number of occasions compared to patients in midazolam group. However the total number of observations made within the acceptable sedation score of 2 to 5 was similar between both the groups as shown in Figure 6.

By 4th hour of study all patients in dexmedetomidine group had achieved adequate sedation while patients in midazolam group did so only near the end of the study. The distribution of inadequate sedation was found to be similar between both the groups. However, patients in midazolam group tended to have excessive sedation

more often than patients in dexmedetomidine group. This was found to be statistically significant.

Recovery from Sedation

The recovery from sedation was significantly rapid in dexmedetomidine group. Patients in dexmedetomidine group were easily aroused and gripped observer's hand earlier after stoppage of sedation. In contrast patients in the midazolam group took a longer time to achieve eye opening on command and gripped observer's hand.

Adverse Effects

Two patients in midazolam group developed respiratory depression at 1 hours of infusion.

Discussion

ICU sedation becomes an integral part in ICU management. Hypnotics most commonly used are propofol, midazolam and lorazepam. Among hypnotics midazolam appeared to be most titratable drug. It has lowest incidence of over and under sedation [5]. Nonpharmacologic and pharmacologic means can be used to provide comfort and safety to ICU patients. The former include communication, frequent reorientation and maintenance of a day-night cycle, noise reduction and ensuring ventilation synchrony. Pharmacologic agents include hypnotic-anxiolytics, opiods, antipsychotics or a combination of these. Over the years, many drugs have been tried for the purpose of sedation of ICU patients.

Now newer drugs are being used for sedation in critically ill patients which have benefits over the conventionally used drugs like midazolam etc. However prolonged use of midazolam has been associated with delayed elimination, accumulation and prolonged sedation even after withdrawal of the drug, especially in elderly patient. Dexmedetomidine, a unique sedative agent, alfa-2 adrenergic agonist, provides proper sedation with analgesia, easy arousability without any respiratory depression. It is now established as a novel approach to intensive care sedation and has the potential to reshape patient care in the ICU and weaning from mechanical ventilation [4]. Its Opiods spairing effects results in reduced opiods-related side effects like respiratory depression, nausea and no risk of physical dependence.

The primary objective of this study was to evaluate the sedation characteristics of dexmedetomidine and midazolam in postoperative mechanically ventilated patients in our ICU. The study was conducted for a period of 24 hours.

In our study, more number of patients in dexmedetomidine group achieved the optimal sedation (Ramsay score 3) earlier and remained for a significantly longer time period than patients in midazolam group. However the acceptable sedation level (Ramsay score 2 to 5) was similar between both the groups. The patients in the midazolam group had significantly more incidences of excessive sedation than patients in dexmedetomidine groups.

The dose of dexmedetomidine used in our study was lower than doses used in earlier studies. For short term sedation of postoperative patients, the dose ranged between 0.2 to 0.7 µg/kg/hr. Our mean dose of midazolam was also lesser than the dose used in many earlier studies. In our studies both the groups had a lower requirement, compared to other studies.

The assessment of the recovery of level of consciousness and weaning time has been favourable to dexmedetomidine in most studies. We did not assess weaning time and time of extubation in our study, only wake up time and time to perform a simple but specific motor function were assessed. Further as a part of our ICU protocol, extubation were avoided in the night time. The length of ICU stay was thus influenced primarily by the underlying disease and not by wake up time. However, our results regarding efficacy and reliability of sedative agents are similar to those reported in the above cited studies.

In our study patients in dexmedetomidine groups were easily aroused and gripped observer's hand earlier than the patients in midazolam group. This difference was found to be statistically significant and could be clinically important when a rapid recovery from sedation is necessary to assess neurologic functions.

In our study both dexmedetomidine and midazolam had a significant fall from baseline values of systolic and mean arterial pressure, the fall being greater in dexmedetomidine group.

We observed a lower heart rate in dexmedetomidine group patients than midazolam group patients. This was consistant with the observations made by others.

The CVP fell more sharply in dexmedetomidine group. This is consistant with the observations made by others.

In our study , both sedative drugs were easy to titrate and infuse through a central line. No patients in either group experienced excitatory effect, wheezing, bronchospasm, hypotention of >20% fall from baseline, flushing or urticaria. The haematological and coagulation values were similar to those at start of study. The screening of biochemical parameters did not demonstrate worsening in renal function or in any of the studied parameters.

Althesin [6] and Etomidate [7,8] were tried for the purpose of sedation but soon fell out of favour because of anaphylactoid reaction and adrenal suppression caused by them. Inhalational agents like nitrous oxide [9] and Isoflurane [10] had limited application in ICU as sedative agents because of ICU environmental pollution and difficulty in the scavenging process of these effects.

Joseph F. Dasta et al [11] studied a cost minimisation analysis of dexmedetomidine compared with midazolam for long term sedation in intensive care unit. They concluded that the dexmedetomidine provides pharmacologic and economic advantage compared with midazolam for mechanically ventilated ICU patients requiring sedation. The reduction in total ICU cost can be explained primarily by decreased costs associated with reduced mechanical ventilation duration and ICU length of stay.

Rchard R. Riker; Yahya Shehabi; Paula M. Bokesch; et al [12], JAMA 2009 compare Dexmedeto-midine and Midazolam for sedation of critically ill patients . They concluded dexmedetomidine-treated patients spent less time on the ventilator, experienced less delirium, and developed less tachycardia and hypertension. The most notable adverse effect of dexmedetomidine was bradycardia.

Jack Depriest et al [13], JAMA 2009 Compared Dexmedetomidine with midazolam for sedation of patients in the ICU. They concluded Patients receiving dexmedetomidine had a lower prevalence of delirium and were extubated almost 2 days earlier than the midazolam group. They believe the safety data from the trial suggest that clinicians should be concerned about using dexmedetomidine in the study's primary patient population, those with severe sepsis.

Jen A. Tan , Kwok M. Ho in 2010 studied Use of dexmedetomidine as a sedative and analgesic agent in critically ill adult patients . They conclude dexmedetomidine might reduce the length of ICU stay in some critically ill patients. The risk of bradycardia was, higher when both a loading dose and high maintenance doses of dexmedetomidine were used.

Although the cost of dexmedetomidine was higher in our study, the ease of titrability, optimal sedation and rapid recovery offered by it makes it a superior choice over midazolam. Cost may not be a concern in situation where sedation needs to be frequently interrupted to assess neurological functions and it is in such circumstances that dexmedetomidine prove to be superior agent. Our use of RSS had some limitations. The scale is a compromise between accuracy, simplicity and ease of use. As a result, most series do not differentiate between sedation, anxiety, depression and pain, but provides an overall patient comfort. Differences between the two drugs may not have become apparent in our study because of low concentrations, short duration of infusion and small sample size.

Conclusion

Both dexmedetomidine and midazolam were effective in providing adequate level of sedation, However dexmedetomidine provided significantely higher occasions of optimal sedation compared to midazolam. Midazolam treated patients tended to remain in excessive sedation on more number of occasions than dexmedetomidine treated patients. Weaning from mechanical ventilation was significantly better in dexmedetomidine than midazolam sedation. Dexmedetomidine treated patients had a significantly better profile of recovery from sedation than patients treated with midazolam. The cost of dexmedetomidine sedation was significantly higher than midazolam sedation.

References

1. Aitkenhead AR, Pepperman ML, Willatts SM et al. Comparison of propofol and midazolam for sedation of critically ill patients. Lancet 1989;11:704-709.
2. Easton C, McKenzie F. Sensory perceptual alterations in the intensive care unit. Heart Lung 1988;17:229-35.
3. Coursin DB, Coursin DB, Maccioli GA. Dexmedeto-midine. Curr Opin Crit care 2001;7:221-226.
4. Ebert JT Current strategies in ICU sedation; Dannenmiller Memorial Education Foundation. 12500 Network Blvd, Suite 101, San Antonio, TX. USA.
5. Bethea JW. Clinical anesthesia, 6th edition. Anesthesiology 2010;112:767–8.
6. Clarke RSJ, Fee JPH Dundee JW. Factors predisposing to hypersensitivity to intravenous anaesthetics. Proc R Soc Med 1977;70:782.

7. Preziosi p, Etmidate, Sedative and neuroendocrine changes. Lancet 1983;ii:276.
8. Watt I, Ledingham IMA. Mortality amongst multiple trauma patients admitted to an intensive therapy. Anaesthesia 1984;39:973-81.
9. Amos RJ, Amess JAL, Hind CJ, Mollin DL. Duodence and pathogenesis of acute megaloblastic bone marrow chagers in patients receiving intensive care. Lancet 1982;ii.835-39.
10. Kong KL, Willatts Sm, Prys-Roberts C. Innsoflurance compared with midazolam for sedation in intensive care unit. Br Med J 1989;298:1277-31.
11. Dasta JF, Kane-Gill SL, Durtschi AJ. Comparing dexmedetomidine prescribing patterns and safety in the naturalistic setting versus published data. Ann Pharmacother. 2004;38:1130–1135.
12. Riker RR, Shehabi Y, Bokesch PM, et al Dexmedetomidine vs Midazolam for Sedation of Critically Ill Patients A Randomized Trial. *JAMA*. 2009;301(5):489–499.
13. DePriest J, Gonzalez L. Comparing Dexmedetomidine With Midazolam for Sedation of Patients in the ICU. *JAMA*. 2009;301(23):2439–2442.
14. Tan JA, Ho KM. Use of dexmedetomidine as a sedative and analgesic agent in critically ill adult patients: a meta-analysis. Intensive Care Med. 2010 Jun;36(6):926-39.