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ORIGINAL RESEARCH ARTICLE

COMPARISON OF DEXMEDETOMIDINE AND MIDAZOLAM INFUSION FOR SEDATION IN PATIENTS ADMITTED IN INTENSIVE CARE UNIT

Lalit Kumar Rajbanshi[1], Batsalya Arjyal[1], Akriti Bajracharya[1], Kanak Khanal[1] Dr Apurb Sharma[2]
[1]Department of Anesthesia and Intensive Care, Birat Medical College and Teaching Hospital Biratnagar, Nepal.
***Correspondence to:** Dr Lalit Kumar Rajbanshi, Department of Anesthesia and Intensive Care, Birat Medical College and Teaching Hospital Biratnagar, Nepal.*
Email: lalitrajbanshi@gmail.com

ABSTRACT

Introduction: Dexmedetomidine and midazolam are frequently used to maintain sedation in mechanically ventilated patient in intensive care unit. The study compared dexmedetomidine and midazolam infusion in mechanically ventilated patient in terms providing effective sedation. **Methods**: This was one year prospective comparative study conducted in 130 mechanically ventilated patients who were randomly divided in two groups receiving either dexmedetomidine or midazolam infusion for sedation. Sedation level was assessed by Riker Sedation-Agitation Scale with the aim of maintaining target sedation score of 3 to 4. The two drugs were compared in terms of sedation level in first 24 hours, time required to achieve target sedation level, hemodynamic changes and adverse effects including ICU delirium. The outcome was measured in terms of duration of mechanical ventilation, length of ICU stays and ICU mortality. **Results**: Both dexmedetomidine and midazolam achieved target sedation level in a comparable time duration. The median sedation level for both the drugs was 4 and 3 in initial 4 and 24 hours respectively. Dexmedetomidne produced significant decrease in blood pressure and heart rate (P=0.044 and P=0.007 respectively). Patients treated with dexmedetomidine had less incidence of ICU delirium (odds ratio=2.669, P=0.029).Dexmedetomidine infusion had signifiicantly shorter duration mechanical ventilation (4.10 ± 2.05 vs. 5.15 ± 2.44, P=0.011), early discharge from ICU (6.05 ± 2.02 vs. 7.48 ± 2.42, p=0.001). ICU mortality was comparable between the groups. **Conclusion**: Dexmedetomidine and midazolam both were equally effective in maintaining sedation in Critically ill patient. Compared to midazolam, dexmedetomidine could be a preferred sedative in ICU in terms of early removal from mechanical ventilation, early discharge from ICU and less incidence of delirium.

Key words: Dexmedetomidine, Mechanical ventilation, Midazolam, Sedation.

INTRODUCTION

Sedation and analgesia are the integral part of management of critically ill patients. Mechanical ventilation, invasive and noninvasive interventions, pain, anxiety are the major external and internal stimuli that make the patient in intensive care unit (ICU) uncomfortable and agitated. Inadequate sedation and analgesia leads to the unnecessary sympathetic activation and has a negative impact on the outcome of critically ill patient.[1] Inadequate sedation can produce patient ventilator asynchrony in mechanically ventilated patients.[2] However, there is tendency to over sedate the patient in order to overcome the negative impact of inadequate sedation which can lead to altered respiratory drive and heamodynamic status, delayed recovery, prolong mechanical ventilation, increase incidence of ventilator associated pneumonia and increase length of ICU stay.[3-5] Sedation and analgesia should be used in a balanced way guided by a frequent clinical monitoring with the aim of achieving stable respiratory and hemodynamic status. Daily interruption of the sedation, using appropriate protocol to deliver spontaneous trial everyday can be effective in early removal of mechanical ventilation. It is recommended to use the valid and reliable sedation assessment tools like Riker Sedation-and Agitation Scale (RSAS) and Richmond Agitation-Sedation Scale (RASS) in order to keep the patient in optimal level of sedation.[6]

There are various protocols to guide the sedation therapy for ICU patients using various pharmacological agents. Dexmedetomidine and midazolam are commonly used ICU sedatives. Midazolam is GABA agonist benzodiazepines, which has been used for many years, as one of the ICU sedative drugs.[7,8] Midazolam is short acting with rapid recovery and minimum respiratory and hemodynamic depression. However, repeated dosing and continuous infusion can lead to prolong sedation and delayed recovery.[9] Because of its well known adverse effect associated with prolong use, the paradigm is changing towards using other non benzodiazepine drugs for ICU sedation. Dexmedetomdine is alpha 2 adrenergic receptor agonist, which acts in the central nervous system producing sedative, anxiolytic, and sympatholytic effect with minimum heamodynamic and respiratory depression. In contrast to benzodiazepines, dexmedetomidine has analgesic action also via spinal cord receptor and hence deceasing the requirement of opioid analgesia. The most recent evidences recommend to use non benzodiazepine sedatives over benzodiazepines in order to improve outcome of the patients in mechanical ventilation.[6]

The dexmedetomidine is newly introduced sedative which is frequently used in ICU of Nepal. To our knowledge, there is not a single study from Nepal comparing dexmedetomidine with midazolam in terms providing effective sedation. So, This study was designed to evaluate and compare the effectiveness of dexmedetomidine and midazolam used as a continuous infusion for sedation in mechanically ventilated patients in ICU of tertiary care hospital of Nepal.

METHODS

This was a prospective comparative study conducted at intensive care unit of tertiary care hospital (Birat Medical College and Teaching Hospital) from 2017 march to 2018 march (one year). Ethical approval was obtained from the ethical board of the hospital. The study was conducted on one hundred and thirty (130) intubated and mechanically ventilated patients of age more than 18 years. The study drug was started within 72 hours of the start of mechanical ventilation. The patients with septic shock with multi organ failure, severe burn, poly trauma, head injury, hepatic failure, renal failure, sever central nervous system pathology, spinal or epidural anesthesia, patients requiring neuromuscular blocking agent were excluded from the study.

The study sample was equally divided into two groups.

Group 1: Dexmedetomidine infusion (n=65 patients)
Group 2: Midazolam infusion (n= 65 patients)

The choice of the drug infusion was made on the basis of computer-generated randomization. The dexmedetomidine was started with a bolus dose of 1 microgram/kg within 10 minutes and then 0.1 to 0.6 µgm/kg/hr as infusion. Similarly, midazolam was used as a bolus dose of 0.05 mg/kg within 1 to 5 minutes followed by continuous infusion with the dose of 1 -2 mg /hr as per needed. During the study period, the analgesia was maintained with non-opioid drugs (acetaminophen) but if needed fentanyl (0.5 to 1 µgm/kg) was added intermittently in a bolus dose. Riker's Sedation Analgesia Scale (RSAS) was used to assess the sedation level. RSAS measures sedation in seven points with score one being the unarousable patients and seven was patients with dangerous agitation.[10] The target sedation score in the study was to maintain within 3 to 4 in the RSAS scale. The infusion dose was titrated accordingly to achieve and maintain the targeted sedation level. The sedation score was assessed clinically with RSAS by the attending nurse every half an hourly till the target sedation level was achieved, there after every four hourly for first 24 hours and then every eight hourly thereafter. Similarly, the hemodynamic parameters like mean arterial blood pressure, heart rate, oxygen saturation were recorded every four hourly for initial 24 hours and the every eight hourly. Any adverse effect like hypotension, bradycardia or desaturation was recorded. The clinical management of the patients was continued as per the instruction of the intensivist on duty. The sedation was interrupted daily to give a trail of spontaneous breathing. The eligible patients were extubated as per the ICU protocol. The total number of days in sedation, duration for mechanical ventilation and length of ICU stay were recorded. Post extubation delirium was assessed and compared by using Confusion Assessment Method for ICU(CAM-ICU) assessment tool.[11]

The investigator who was recording all the study observations and the patients were not aware of the

infusion drugs. The primary outcome of the study was to assess and compare the sedation level of the two drugs. The secondary outcome was to compare the hemodynamic changes, adverse effect of the sedative drugs, length of mechanical ventilation and ICU stay and 30 days mortality between the two groups receiving the two drugs.

Statistical Analysis;
Rikers RR et al had observed that the absolute difference in the percentage of time within target RASS range was 2.2%.[12] We assumed that 15% of difference in our study would produce a statistically significant difference in the sedation level between the two drugs. We considered 5% as type I error and 80 % of power of study and taking 10 % as drop out sample, the sample size was calculated to be 65 in each group.

The data were recorded in Microsoft excel and statistical analysis was done by IBM SPSS version 21. The categorical data were presented as percentage and frequency while continuous data was presented as mean, median and standard deviation. Chi Square test was used for categorical data while Mann Whitney test were used for continuous data. P value less than 0.05 was considered statistically significant.

RESULTS

Total of one hundred thirty patients participated in the study. However, three patients from group 1 (dexmedetomidine group) and five patients in group 2 (midazolam group) were excluded from the study after the start of infusion due to the reasons like death within 24 hours, hemodynamic instability, development of multi organ failure.

The age, weight and sex of the participants were comparable between the two groups (P>0.05). The mean age in group 1 was 41.53 ± 15.08 (SD) while it was 44.12 ± 17.41(SD) in group 2. Similarly, the mean weight was 63.16 ± 14.35 and 64.72 ± 15.04 kg in group 1 and 2 respectively. Male and female participants were equally distributed between the groups.

The bolus dose of the study drugs was followed by the continuous infusion in order to achieve the sedation score of 3 or 4. The sedation level was assessed with RSAS scale every half an hour till the target score was achieved and then every four hourly for 24 hours. The mean durations to achieve the target sedation level were 67.23 ± 18.77 minutes and 66.53 ± 20.81 minutes for dexmedetomidine and midazolam respectively with P value more than 0.05. Similarly, the mean duration of infusion of dexmedetomidine was 5.00 ± 2.83 days while it was 5.18 ± 2.61 days for midazolam.

The box plot of the sedation level assessed by RSAS at 4 and 24 hours were shown in **figure 1 and 2**. At four hours, the median sedation score was 4 for both the drugs. However, midazolam infusion had wide range of sedation score at 4 hours (2 to 7) compared to dexmedetomidine infusion (2 to 5). Similarly, at 24 hours, the median sedation score was 3 for both the drugs. At this point of time, midazolam infusion provided deep level of sedation in majority of the patients (range 1 to 4).

Group 1 – Dexmedetomidine infusion, Group 2- midazolam infusion

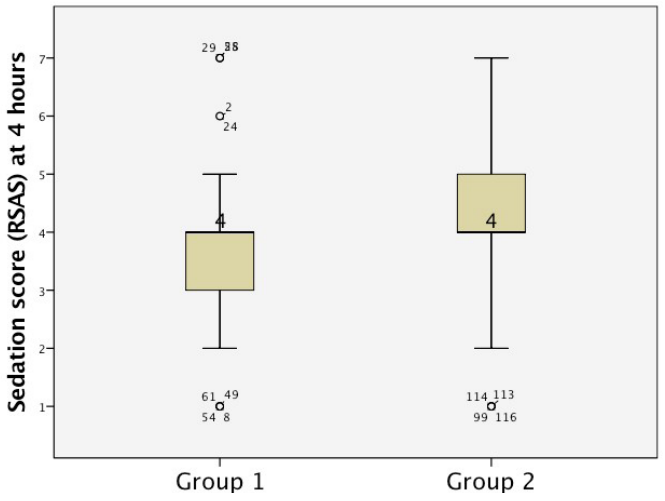

Figure 1: Boxplot for sedation level (RSAS Score) at 4 hours of infusion

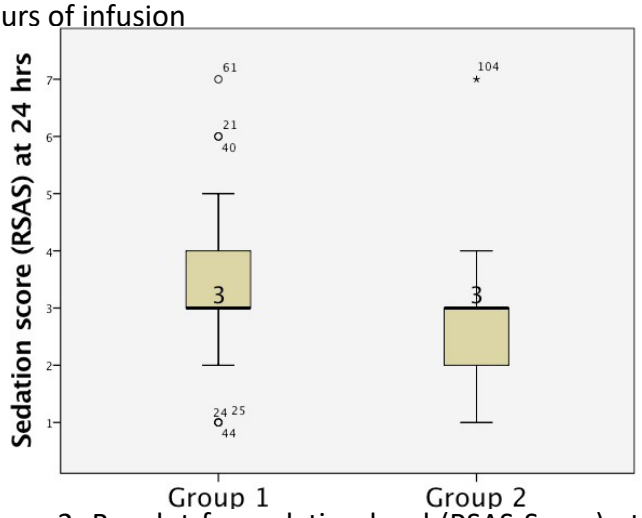

Figure 2: Boxplot for sedation level (RSAS Score) at 24 hours of infusion

The mean arterial blood pressure, mean heart rate and mean oxygen saturation (SP02) were compared between the groups and were shown in figure 3,4,5 respectively. The dexmedetomdine infusion produced greater fall in blood pressure and the heart rate as compared to midazolam infusion. There was maximum decrease in blood pressure and heart at 12 to 16 hours of infusion and the difference between the groups was statistically significant (P< 0.001). The oxygen saturation was comparable between the groups.

The incidence of adverse effects like hypotension, bradycardia and delirium were compared betwwen the two drugs and shown in table 1. The outcome of the infusion therapy in terms of duration of mechanical ventilation, length of ICU stay and 30 days mortality was presented in table 2. The patients receiving midazolam infusion were 0.455 times (OR) less likely to have hypotension as compared to patients receiving dexmedetomidine and the difference was statistically significant (P=0.044). Similarly bradycardia was more frequent in dexmedetomidine patients (18.9% vs. 7.4% with odds ratio 0.299,CI 95% 0.125-0.719, P= 0.007). Post extubation delirium was more common in patients receiving midazolam infusion 13.9%, (P= 0.029, OR=2.69 ,CI 95%, 1.052- 6.770).

Table 1: Comparison of adverse effects of dexmedetomidine and midazolam

Variables	Group 1 (n=62)	Group 2 (n=60)	Odds ratio	CI 95%		P Value
				L	U	
Hypotension	22 (18%)	12 (9.8%	0.455	0.20	1.03	0.044
Bradycardia	23 (18.9%)	9 (7.4%	0.299	0.12	0.71	0.007
Delirium	8 (6.6%)	17 (13.9%)	2.669	1.05	6.77	0.029

Note: Group 1 – Dexmedetomidine infusion, Group 2- midazolam infusion

Table 2: Comparison of outcome variables.

Variables	Group 1 (n=62)	Group 2 (n=60)	P value
Duration of MV (days)	4.10 ± 2.05	5.15 ± 2.44	0.011
Length of ICU stay (Days)	6.05 ± 2.02	7.48 ± 2.42	0.001
Mortality	5 (4.1%)	7 (5.7%)	0.556 OR 1.5 (CI 95%, 0.45- 5.03)

Note: Group 1 – Dexmedetomidine infusion, Group 2- midazolam infusion

The dexmedetomidine infusion produced significantly shorter duration of mechanical ventilation as compared to midazolam infusion (4.10 ± 2.05 days vs. 5.15 ± 2.44, P= 0.011). Similarly, length of ICU stay was also significantly shorter for the patients receiving dexmedetomidine infusion (P= 0.001). The 30 days mortality was comparable between the two groups (P=0.556) with the midazolam group 1.5 times more likely to have increased mortality as compared to dexmedetomidine group.

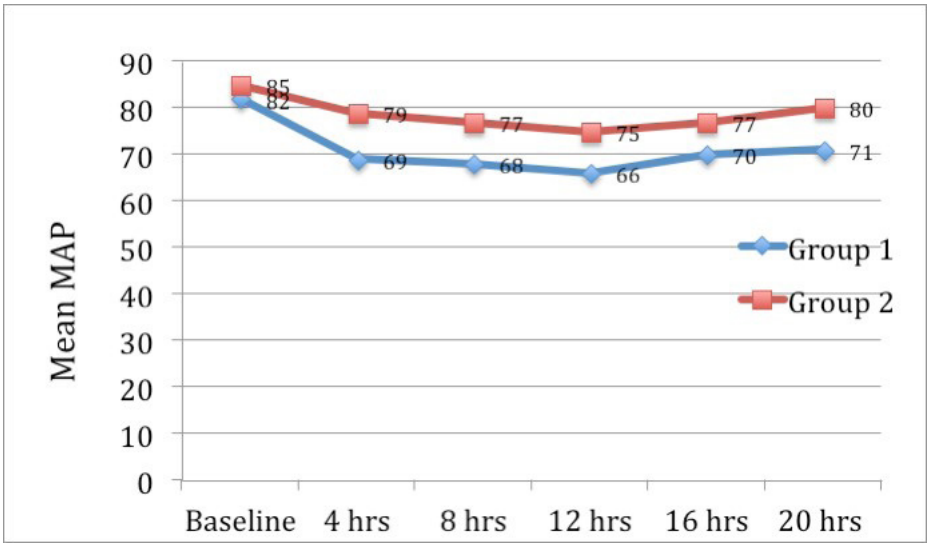

Figure 3: Comparison of mean arterial pressure (MAP) between two groups in first 24 hours
Note: Group 1 – Dexmedetomidine infusion, Group 2- midazolam infusion

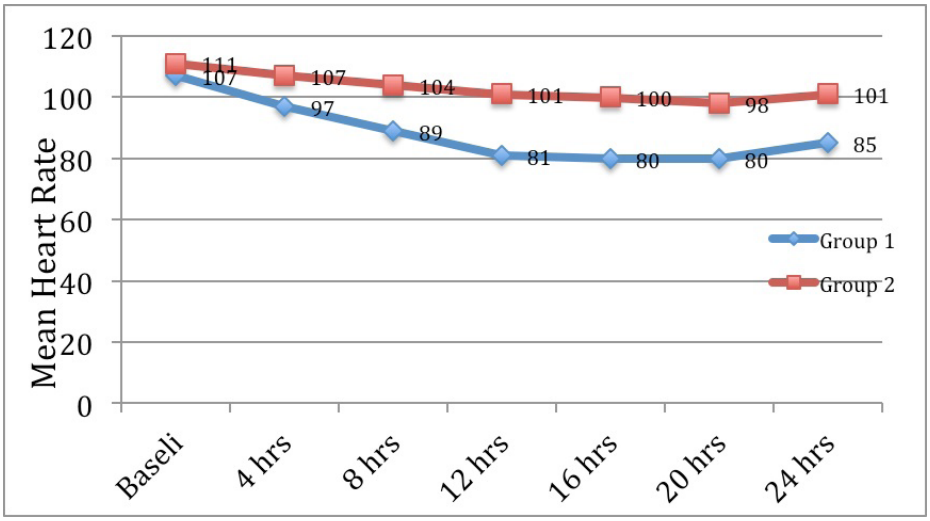

Figure 4: Comparison of heart rate between two groups in first 24 hours
Note: Group 1 – Dexmedetomidine infusion, Group 2- midazolam infusion

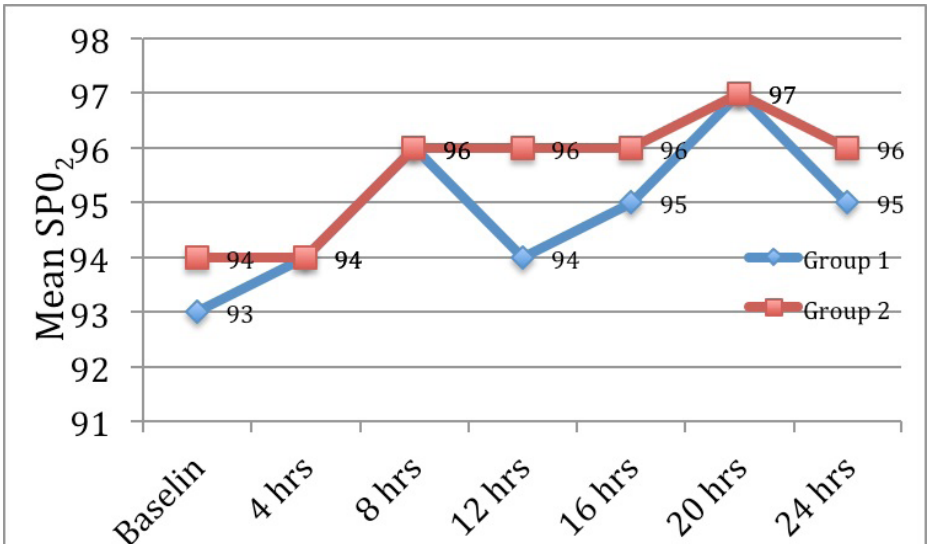

Figure 5: Comparison of oxygen saturation between two groups in first 24 hours
Note: Group 1 – Dexmedetomidine infusion, Group 2- midazolam infusion

DISCUSSION:

Critically ill patients in ICU should be managed with adequate and effective sedation and analgesia. Dexmedetomidine and midazolam are the two important sedative drugs that have been used very frequently to achieve adequate sedation for critically ill patients. The present study had compared the effect of dexmedetomidine and midazolam infusion for ICU sedations.

The primary outcome of the study was to compare the sedation level in first 24 hours. The target sedation score assessed by RSAS scale was achieved in comparable time duration in both the study drugs. The median score for sedation level was 4 at 4 hours and 3 at 24 hours for both the drugs. The results of the study were in contrast to the previous studies where dexmedetomidine infusion had achieved the sedation score more frequently.[13,14] The infusion of the sedative drugs was interrupted daily to assess the patient for the readiness of spontaneous breathing trial. Moreover the sedation level was frequently assessed initially every half an hourly till the adequate sedation level was achieved and then every 4 hourly for 24 hours. These might be the possible reason for the comparable sedation level between dexmedetomidine and midazolam.

Dexemedetomidine provided a comparatively narrower range of sedation level (2 to 5) than midazolam infusion (2 to 7) and at the end of 24 hours the range of the sedation score for the patient in dexmedetomidine infusion was again 2 to 5 while it was 1 to 4 in midazolam group producing deep sedation in group 2 patients. Thus dexmedetomidine provided a uniform pattern of sedation level in comparison to midazolam. Besides having sympatholytic and sedative actions, dexmedetomidine has got additional analgesic properly via the receptors in spinal cord.[15] The analgesia provided by the dexmedetomidine along with sedation had contributed in achieving more uniform pattern of sedation level in group 1 patients.

It was observed that the decrease in mean arterial blood pressure and heart rate was more in dexmedetomidine infusion than midazolam infusion. Oxygen saturation was comparable between the groups. Richard R Riker had demonstrated that patients treated with dexmedetomidine were more likely to develop bradycardia with a nonsignificant increase in the proportion requiring treatment and less likely to develop hypertension.[12] In our study, patients treated with dexmedetomidine were 2.1 and 3.3 times more likely to develop hypotension and bradycardia respectively. Similar results where dexmedetomidine produced significant bradycardia and hypotension were also seen in various other studies.[16-18] Dexmedetomidine caused marked decrease sympathetic activity which significantly decreased heart rate and mean arterial blood pressure. The analgesic property provided by the dexmedetomidine might have provided more stable hemodynamics. Absence of additional analgesic property in midazolam might have led to increase sympathetic activity and less control on hemodynamics.

The patients treated with dexmedetomidine were 0.374 less likely to develop delirium as compared to midazolam. This finding was supported by the study done by Richard R Riker et al. where they had found very few patients with dexmedetomidine had developed ICU delirium.[12] Delirium is one of the acute reversible cognitive dysfunctions that can have negative impact on the outcome of the patient. The use of sedatives especially benzodiazepines is one of the major etiological factor for the ICU related delirium.[19] Dexmedetomidine significantly decrease the incidence of ICU related delirium as well as it can be effectively used for the treatment of delirium.[12, 15]

It was observed that the dexmedetomidine infusion for sedation had led to significantly shorter duration of mechanical ventilation and early discharge from ICU. Dexmedetomidine has unique advantage of providing arousable sedation maintaining uniform depth of sedation. Moreover, the sedation was interrupted daily to make the patients awake for spontaneous breathing trail. Richard R Riker et al had clearly demonstrated that the patient treated with dexmedetomidine had earlier weaning and removal from mechanical ventilation.[12] Similarly, the SPICE investigators from New Zealand and Australia had found that the deep sedation was the independent predictor of longer duration of mechanical ventilation and increased mortality.[20] In this regard dexmedetomidine was found to be effective in providing light plane of sedation. Early spontaneous breathing trail, early removal of the mechanical ventilation had led to early discharge from ICU in patients receiving dexmedetomidine. As

the result showed the patients receiving midazolam were deeply sedated at the end of 24 hours (sedation level ranging from 1-4 at 24 hours), which might be the possible reason for delayed awakening and longer stay in mechanical ventilation and in ICU.

The 30 days mortality was comparable between the groups and none of the death was related to the use of either of the sedative drugs. However, patients receiving midazolam were 1.5 times more likely to have increased mortality as compared to dexmedetomidine due to the increased morbidity caused by deeper sedation, increased duration in mechanical ventilation and longer ICU stay.

Now a days light plane of sedation is better preferred for critically ill patients. This paradigm of ICU sedation keeps the patient well sedated in mechanical ventilation and in the other hand, makes the patients awake and ready for extubation at the earliest moment. Dexmedetomidine is the preferred choice of sedation over benzodiazepine in this regard as it provides minimum adequate light sedation with analgesia as well as less respiratory depression and less post extuation delirium.

LIMITATIONS:

The study had evaluated the sedation level only in the first 24 hours of starting infusion. This might have potentially biased the result in favor of dexmedetomidine. Measuring sedation level through out the infusion duration might have produced a more reliable outcome. Midazolam is short acting benzodiazepines and was used as a comparator drug as this this the most commonly used sedative in ICU. However, the long-term use of midazolam has potential to deposit in the body fats, which might have confounded the study outcome. Delirium reported in the study could not be solely contributed by the study drugs only because there are various other factors like sleep deprival, medication, electrolyte imbalance which were not assessed in the study.

CONCLUSION:

The outcome of critically ill patients can be improved with adequate level of sedation. Both dexmedetomidine and midazolam were considered equally effective in achieving adequate level of sedation for critically ill patients. Dexmedetomidine provided light plane of sedation that helped to make the patient awake earlier. Patients treated with dexmedetomidine had earlier weaning and removal from mechanical ventilation, shorter ICU stay and less chance of developing ICU delirium. Thus, dexmedetomidine can be a preferred sedative drugs over midazolam in achieving effective sedation with better outcome.

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