Comparison between Dexmedetomidine and Midazolam with Validation of BIS for Sedation in Mechanically Ventilated ICU Patients

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INTRODUCTION

Sedation is an essential component of the management of intensive care patients. It is required to relieve the discomfort and anxiety caused by procedures such as tracheal intubation, ventilation, suction and physiotherapy. Inadequate sedation can result in hyper catabolism, immunosuppression, hypercoagulability, increased sympathetic activity that are associated to a significant outcome impairment. On the other hand, over sedation can increase time on ventilator support, so exacerbating the risk of lung damage and neuromuscular alterations and increasing ICU stay therefore continuous monitoring of sedation is essential.

In order to avoid these cumbersome problems, many instrumental tools of sedation monitoring have been proposed for direct evaluation of the central nervous system actions of sedative drugs. Among EEG derived parameters, Bispectral Index (BIS) is now an accepted tool for the evaluation of CNS sedative drugs effect. The bispectral index is a statistically based, empirically derived complex parameter. It is a weighted sum of electroencephalographic sub parameters, including a time domain, frequency domain, and high order spectral sub parameters.

There are several drugs used for sedation in ICU two drugs used in our study are Dexmedetomidine and Midazolam. Dexmedetomidine was approved by the Food and Drug Administration at the end of 1999 for use in humans as a short-term medication (<24 hours) for analgesia and sedation in the intensive care unit (ICU).

As of 2010, Midazolam is the most commonly used benzodiazepine in anaesthetic medicine. Intravenous midazolam is indicated for procedural sedation (often in combination with an opioid, such as fentanyl), for preoperative sedation, for the induction of general anaesthesia, and for sedation of ventilated patients in critical care units.

MATERIAL AND METHOD

The present study was a prospective study carried out in ICU of MGH hospital attached to Dr. S. N. Medical College Jodhpur after obtaining Institutional ethical committee approval and written informed consent. The aim of this study was to compare the effects of Dexmedetomidine & Midazolam on sedation, hemodynamic in mechanically ventilated intensive care patients and to verify the clinical validity, reliability, and applicability of BIS for monitoring sedation in mechanically ventilated ICU patients searching for a correlation with the Ramsay score.

This study was conducted on a total number of 60 patients on mechanical ventilator given sedation for 12 hours. On the patient arrival to ICU complete medical history and physical examination (general systemic examination) of the patient was carried out, baseline measurements was completed including vital signs (HR, BP, SPO2), 12-lead ECG, chest x-ray, blood samples (blood gases, haematology, and blood biochemistry), ventilation variables, APACHE II score.

The patients were further divided into 2 groups, each group consist of 30 patients as follows:

Group A (30 patients): Received dexmedetomidine at loading dose of 1 microgm/kg over 10 min followed by a maintenance infusion of 0.5 microgms/kg/hr(0.2-0.7 microgms/kg/hr)

Group B (30 patients): Received midazolam at loading dose of 0.05mg/kg over 2 min followed by a maintenance infusion of 0.03mg/kg/hr(0.02-0.05mg/kg/hr) Both group patients received fentanyl at 1 microgm/kg prior to the study drugs.
The degree of sedation was measured and recorded hourly using Ramsay sedation score (RSS) and continuously using the bispectral index (BIS), and level 4-5 of Ramsay scale is taken as target for sedation. Ramsay scores was compared with the average of BIS values obtained 60 seconds before and the 60 seconds after the stimulus application.

Hemodynamically stable patients between 18 and 80 years who required sedation and mechanical ventilation for >=6 hours were included.

In both group the target was to achieve and maintain RSS Score of 4-5 & to monitor & record BIS value accordingly. If the aimed RSS level was not achieved or maintained by the study drug (dexmedetomidine at its maximum dose at 0.7microgms/kg/hr for 1hour period & midazolam at its maximum dose at 0.05mg/kg/hr for 1 hour) alone, the study drug was supplemented by propofol bolus with 0.2mg/kg for maximum three successive bolouses at an interval of 3-5 min thereafter if the desired RSS level was not achieved the case was labelled as failure. Ventilator setting, FiO2 & PEEP was adjusted according to ARD Snet ventilator strategy/protocol & to keep SPO2 between 88-95%.

Vital signs (heart rate, mean blood pressure, mechanical ventilation mode, FiO2, PEEP) was monitored continuously and recorded every 10 mins during the first hour and every 60 mins from 1 hour after until the end of study drug infusion i.e. 12 hour. Throughout the study, each patient was monitored for clinical or laboratory evidence of adverse events.

Descriptive statistics were used to describe the baseline characteristics. Dichotomous outcomes were compared by Chi square test with continuity correction or Fisher’s exact test as applicable. Numerical variables were compared by Student’s t test or Mann Whitney U test, depending on distribution. Intra-group comparison was done using Repeated Measure ANOVA. Analysis was intention to treat, i.e., all subjects who were randomized were included in analysis, irrespective of degree of compliance. Analysis was done using SPSS version 17. The results were considered significant when the p value was < 0.05.

RESULTS

Baseline characteristics were comparable in both the groups. Table 1 shows the demographic profile of both groups. The mean age in group A was 43 years, in group B was 48 yrs. The mean weight in group A was 67 kg and in group B was 61 kg. The APACHE Score in group A was 16 and in group B was 15. All these differences were statistically not significant.

<table>
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<th>Group Statistics</th>
<th>Group</th>
<th>N</th>
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<th>Std. Deviation</th>
<th>Std. Error Mean</th>
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<td>t-1.113 P&gt;0.05</td>
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<td></td>
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</table>

COPD patients in group A & group B was same 6 patients each. P/O ABDOMINAL SURGERY patients in group A was 11 compared to 8 in group B. POISONING patients in group A was 4 compared to 6 patients in group B. SEPTICEMIA patients in group A was 3 compared to 4 patients in group B. OTHERS in groups A and in group B was 6.

Baseline investigations were comparable in both the groups. The mean Hb in group A was 11.9, in group B was 12.1. The mean PaCO2 in group A was 46.1 mm of Hg and in group B was 43.7 mm of Hg. The mean PaO2 in group A was 108.8 mm of Hg and in group B was 114.7 mm of Hg. The mean Na+ in group A was 141.8 meq/l and in group B was 141 meq/l. All these differences were statistically not significant. Table 2: shows the baseline investigations in two groups.
Baseline parameters were comparable in both the groups. The mean HR in group A was 106 in group B was 110. The mean MAP in group A was 95 mm of Hg and in group B was 93 mm of Hg. The mean SpO2 in group A was 98% and in group B was 98.5%. The mean RR in group A was 22 and in group B was 18. All these differences were statistically not significant. Table 3: shows the baseline parameters in two groups.

Parameters before loading dose were comparable in both the groups. The mean HR in group A was 105 and in group B was 110. The mean MAP in group A was 95 mm of Hg and in group B was 93 mm of Hg. The mean SpO2 in group A was 97.8% and in group B was 98.5%. The mean FiO2 in group A was 51% and in group B was 53%. The mean PEEP in group A was 5 and in group B was 6. The mean BIS in group A was 89 and in group B was 91. The mean RSS in both groups A and B was 1. All these differences were statistically not significant.

Table 3 shows the parameters after loading dose in two groups. The mean HR in group A was 86 and in group B was 105 with p value <0.05, which was statistically significant. The mean MAP in group A was 90 mm of Hg and in group B was 89 mm of Hg. The mean SpO2 in group A was 98.4% and in group B was 98.7%. The mean FiO2 in group A was 51% and in group B was 53%. The mean PEEP in group A was 5 and in group B was 6. The mean BIS in group A was 55 and in group B was 59 with p value <0.05, which was statistically significant. The mean RSS in group A was 5 and in group B was 4 with p value <0.05 which was statistically significant.

Fig 1 shows the comparison of heart rate at different time interval in two groups. The heart rate in two groups was having significant statistical difference at all time interval with p value <0.05. Data shows that heart rate in group A was lower than group B.
The mean arterial pressure at different time interval in two groups. All values in both groups were comparable with statistically no significant difference.

Correlation between Ramsay sedation score (RSS) and average Bispectral index (BIS) at different time interval in group A patients was done. Applying pearson test, found an average r value of \( -0.913 \) (pearson correlation coefficient at different time interval in group A between average BIS and RSS score with value of \( r \) is between \(-0.819\) to \(-0.956\).) in group A between RSS and average BIS in which \((-\) sign indicate an inverse relation, as RSS increase BIS decreases and vice versa. Data shows significant correlation between RSS and average BIS with p value <0.01.

Similar correlation between Ramsay sedation score (RSS) and average Bispectral index (BIS) at different time interval in group B patients was also done. Applying pearson test, found an average r value of \( -0.912 \) (average BIS and RSS score with value of \( r \) is between \(-0.738\) to \(-0.973\). Data shows significant correlation between RSS and average BIS in group B between RSS and average BIS in which \((-\) sign indicate an inverse relation, as RSS increase BIS decreases and vice versa. Data shows significant correlation between RSS and average BIS with p value <0.01.

**Line diagram 2:** shows comparison between pearson correlation coefficient of group A and group B at different time interval during sedation.
The mean BIS value for different RSS score in group A and Group B patients was calculated. At In Group A patients, RSS score 4 mean BIS was 66(66.4) and at RSS score 5 mean BIS was 58(57.8) and Data shows as RSS score increases the BIS value decreases and vice versa.

In Group B patients RSS score 4 mean BIS was 66(66.2) and at RSS score 5 mean BIS was 57 in group B patients. Data shows as RSS score increases the BIS value decreases and vice versa.

**Line diagram3:** shows comparison between the average mean BIS value with RSS score in group A and group B. In both group value of mean average BIS to RSS score are comparable with both groups showing significant correlation between average BIS value and RSS score.
Use of rescue drug propofol during sedation in both group patients was calculated. In group A out of 30 patients 11 patient required propofol and in group B 19 patients required propofol. Applying Chi-square test shows 4.267,1. P value is 0.0398(<0.05) which is statistically significant. Data shows group B patients required more propofol for maintaining sedation level then the patients in group A.

Adverse event was seen during sedation in both groups. In group A out of 30 patients 4 had bradycardia and in group B no patients had bradycardia. In both group hypotension was not observed.

**DISCUSSION**

Providing sedation for patient comfort is an integral component of bedside care for nearly every patient in the intensive care unit (ICU). Inadequate sedation techniques may adversely affect the morbidity and mortality in intensive care unit and search for ideal sedative agent continues.

For decades, gama aminobutyric acid (GABA) receptor agonists (including propofol and benzodiazepines such as midazolam) have been the most commonly administered sedative drugs for ICU patients worldwide. Newly released clinical practice guidelines insist on the monitoring of sedation as an emerging standard of care. Among these BIS have been proposed to evaluate the depth of anesthesia during surgery and then used in ICU to monitor sedation level. Sigl and Chaumon in a review of the main features of BIS, concluded that, in general, a BIS score of 100 reflects the awake state, 80 reflects some sedation, 60 reflects a moderate hypnotic level and 40 a deep hypnotic level.

We conducted a prospective randomized control study to compare iv dexmedetomidine and iv midazolam for sedation and hemodynamic in mechanically ventilated ICU patients and to verify the clinical validity, reliability, and applicability of BIS for monitoring sedation in ICU patients searching for a correlation with the Ramsay score. There was no dropout recorded throughout the study.

Random sampling made the distribution of the patients in all groups comparable. A similar pattern and primitive study forced us not to land in any trouble. Therefore any situation, which should have complicated the course of sedation, was avoided.

In our study there was even distribution of age and weight in two groups. In a similar type of study carried out by R.M.Veen, Andreas E. Triltsch, Richard R-Ricker there were no statistically significant difference between the two groups with respect to age. Therefore, clinically insignificant variations in age simply helped us to alleviate these confounding factors, like distribution metabolism, excretion and action of different drugs and clinically insignificant variations in weight simply helped us to alleviating a point of controversy because obesity as well as cachexia has clinically significant effect on the clinical action of drug.

The APACHE score was comparable in both A and B group which was statistically insignificant, as in study carried out by Richard R-Ricker in which the mean APACHE score of patients in dexmedetomidine and midazolam.

Baseline investigations were comparable in both the groups which was statistically insignificant as in the study carried out by R.M.Veen, Andreas E. Triltsch, Richard R-Ricker.

Baseline mean HR was almost similar in two groups. After loading dose, there was significant decrease in heart rate in group A (86.8+26.2) compare to group B (105+19.51) with p value <0.05 which was statistically significant. Total duration of sedation was 12 hours with heart rate monitored every 10 min during first hour of sedation than hourly until the end of sedation period. It means that the patients sedated with dexmedetomidine had significant lower heart rate compared to patients sedated with midazolam. Both Richard R. Riker and Esmaoglu in 2009 and Wan LJ in 2011 found Dexmedetomidine treated patients were more likely to develop bradycardia.

In our study the total duration of sedation was 12 hours with MAP monitored every 10 min during first hour of sedation than hourly until the end of sedation period and found statistically no significant difference with p value >0.05 as similar to found by Wan LJ, in 2011.

In a similar study by Esmaoglu in 2009 observed mean arterial blood pressures were similar in the two groups (P > .05), although in the dexmedetomidine group, it was lower at 5, 6, 12, and 24 hours compared with the first 4 hours (P < .05). In our study the target of sedation was to keep the Ramsay sedation score at 4 or 5 in both groups and to correlate the score with BIS. We observed that the desired level of sedation was achieved in both the groups but in group A, patients were aroused easily with adequate sedation, when compared with the group B patients and also in group B patients the use...
of rescue drug propofol compared to group A for achieving the desired RSS was more. Richard R. Riker\textsuperscript{\textregistered} in 2009 found that there was no difference in the time patients spent within the sedation target range with dexmedetomidine or midazolam. Applying the pearson test we found an ‘r’ value of -0.9125 considering all patients of both groups and respectively of -0.913 and -0.912 in group A and group B separately. Between Ramsay score and BIS, increase of the Ramsay score there was a progressive decrease in the BIS score (Ramsay score = 2, BIS = 84.36, 85.9+5.9 in group A and group B respectively; Ramsay score= 4,BIS=66.43+3.2, 66.2+3.1; Ramsay score=5,BIS=57.8+3.4, 57.45+3.1; Ramsay score = 6, BIS= 45.2+4.7, 43.8+2.8 in group A and group B respectively) as found by Epifanio Mondello\textsuperscript{\textregistered} and Mondello et al\textsuperscript{\textregistered}. De, Deyne et al also observed a good correlation between BIS and the Ramsay scale in 18 ICU patients sedated with midazolam to a Ramsay score of 6.

**CONCLUSION**

In our study we found that, similar level of sedation was achieved by both dexmedetomidine and midazolam. At comparable sedation levels, dexmedetomidine-treated patients were aroused easily with adequate sedation and required less propofol. The most notable adverse effect of dexmedetomidine was bradycardia which was in acceptable limit.

In conclusion, the data obtained from the study, seems to validate BIS monitoring for ICU sedation. BIS monitoring can be useful in defining an appropriate sedation level in ICU patients while still maintaining the use of the score systems for care for ICU patient.