## ORIGINAL ARTICLE

# A COMPARATIVE STUDY OF MIDAZOLAM, PROPOFOL AND DEXMEDETOMIDINE INFUSIONS FOR SEDATION IN MECHANICALLY VENTILATED PATIENTS IN ICU

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## ABSTRACT

**Background**: This study was aimed to compare the sedative properties of study drugs- midazolam, propofol and dexmedetomidine in critically ill patients with GCS of 12-15 on invasive mechanical ventilation.

**Methodology**: This study was carried out in 75 adult patients with Glasgow coma scale score of 12-15, on mechanical ventilation. The study patients were divided into 3 groups with each group consisting of 25 patients- Group M received inj. Midazolam loading dose 0.15mg/kg intravenous followed by continuous infusion of 0.02-0.1mg/kg/hr, Group P received inj. Propofol loading dose 1.5mg/kg intravenous followed by continuous infusion of 1-6 mg/kg/hr and Group D received inj. Dexmedetomidine loading dose 1μg/kg intravenous followed by continuous infusion of 0.2-0.7 μg/kg/hr. All patients were given study drug infusion for 48 hours to achieve Richmond Agitation Sedation Scale Score 0 to -2. Assessment of RASS score, mean pulse rate, mean arterial pressure, total respiratory rate and $SpO_2$ were monitored initially at 5 min interval after the loading dose is given, till 30 minutes, then at 1st hour and 2nd hour, then at 6th hour and 12th hour, then every 12th hour till 48 hour.

**Results:** The mean pulse rate and mean arterial pressure decreased after giving loading dose in all three groups and it was more in dexmedetomidine group which continued to be significant till 20 and 30 minutes respectively. RASS remained in the target range of 0 to -2 in all the three groups throughout the sedation period of 48 hours by their infusion doses.

**Conclusion:** With dexmedetomidine similar levels of sedation can be achieved as compared to propofol and midazolam. All the three drugs are equally efficacious in regard to cardiorespiratory stability in maintaining target sedation (RASS 0 to -2) in mechanically ventilated patients in ICU.

**Key words:** Midazolam, Propofol, Dexmedetomidine, Infusions, Mechanical Ventilation, Sedation, ICU.

## INTRODUCTION

One of the key factors for good clinical practice in the intensive care unit is to provide sedation to ensure patient comfort. Sedation in intensive care patient is assumed to reduce discomfort from critical care interventions, to increase tolerance of mechanical ventilation, to prevent accidental removal of instrumentation, to suppress cough response to prevent fighting against ventilator and to reduce metabolic demands during cardiovascular and respiratory instability.[1] The fight against ventilator causes dyssynchrony between patient and ventilator which leads to anxiety, tachycardia, high blood pressure, lung injury (ALI) to the patient. This causes prolongation of intensive care unit stay, increases the cost and worsens the prognosis of the patient. The goal of sedation in ICU is to have a cooperative and reasonably calm patient who will not harm himself or interfere with ICU care.[2]

Ideal sedative agent for sedation in ICU patients should have the properties like rapid onset and offset of action, minimal cardiovascular side effects, controllable respiratory side effects, no accumulation in renal or hepatic dysfunction, inactive metabolites, cheap in cost and no interaction with other intensive care unit drugs. No drug with all these properties exist and therefore there is a need to find a better agent which has maximum properties meeting the ideal sedative agent for use in patients on ventilator.[3]

This study was intended to find effectiveness and potency, haemodynamic stability, safety and occurrence of any complication of the three commonly used sedative drugs propofol, midazolam and dexmedetomidine in mechanically ventilated patients in need of moderate sedation in ICU set up.

## METHODOLOGY

Approval from ethical committee of Government medical college and associated group of hospitals, Kota, (Raj.), India was obtained for this study. Written informed consent from all the patient's attendant were obtained. This prospective randomized clinical study was carried out in 75 adult patients with Glasgow coma scale score of 12-15, who were on mechanical ventilation in clinical need for light to moderate sedation. Patients with severe neurological disorder with GCS< 12, mean arterial pressure less than 50 mmHg despite appropriate volume replenishment, heart rate <50/min, with renal or hepatic failure, or sensitivity with any of study drug were not included in this study. Patients who died even after critical care were not included in this study.

Patients were divided into three groups of 25 each. Group M patients received IV inj. Midazolam loading dose 0.15mg/kg followed by maintenance dose of 0.02-0.1mg/kg/hr by continuous infusion by infusion pump. Group P patients received intravenous inj. Propofol loading dose of 1.5mg/kg followed by continuous infusion of 1-6 mg/kg/hr. Group D patients recieved intravenous inj. Dexmedetomidine loading dose of 1μg/kg followed by maintenance dose of 0.2-0.7 μg/kg/hr of continuous infusion by infusion pump. All the patients received inj. Tramadol 100 mg TDS intravenous every 8 hourly. Desired depth of sedation was assessed by RASS score.[4] All the patients were given study drug bolus and then infusion for 48 hours to keep Richmond Agitation Sedation Scale Score 0 to -2. Tidal volume was set to 8 ml/kg. Mode of ventilation was set to SIMV.

RASS score, mean pulse rate, mean arterial pressure, total respiratory rate and SpO2 were noted initially at 5 min interval after the loading dose till 30 minutes, then at 1 hour and 2 hour, then at 6th hour and 12th hour and then every 12th hour till 48 hour. Complications like bradycardia (PR<60/min), hypotension (MAP<60 mmHg), respiratory depression, etc. were closely observed and managed accordingly.

**Statistical analyses:** All results were expressed as mean ± SD (standard deviation). ANOVA (One-Way Analysis of Variance) test was used for independent variables with normal distribution. Microsoft Excel 2007 with SPSS Statistics software used for statistical analysis. P<0.05 was considered statistically significant.

## RESULTS

There were no significant difference in demographic data and diagnosis/reason for mechanical ventilation, between the three groups as shown in table 1 and 2.

**Table 1: Demographic Profile**

| Variable | Group D (Mean±SD) | Group M (Mean±SD) | Group P (Mean±SD) |
|---|---|---|---|
| Age (yrs) | 37.16±2.468 | 35.96±2.29 | 38.76±2.522 |
| Wight(kgs) | 62.76±1.89 | 63.36±1.833 | 64.12±1.95 |
| Sex(M/F) | 15/10 | 16/9 | 15/10 |

**Table 2: Diagnosis of patients requiring endotracheal intubation and SIMV mode of ventilation**

| DIAGNOSIS | Group D (%) (N= 25) | Group M (%) (N=25) | Group P (%) (N=25) |
|---|---|---|---|
| **ARDS** | 3 (12) | 3 (12) | 4 (16) |
| **Acute exacerbation of copd** | 7 (28) | 6 (24) | 7 (28) |
| **Aspiration pneumonitis** | 6 (24) | 4 (16) | 5 (20) |
| **Acute LVF** | 1 (4) | 2 (8) | 1 (4) |
| **Post operative respiratory depression** | 4 (16) | 4 (16) | 3 (12) |
| **Seizures** | 3 (12) | 4 (16) | 4 (16) |
| **Snake bite** | 1 (4) | 2 (8) | 1 (4) |

**Table 3: Comparison of mean pulse rate (/min) at different time interval ( in MEAN±SD)**

| TIME | GROUP D | GROUP M | GROUP P | p-Value |
|---|---|---|---|---|
| PRE SEDATION | 104.8± 9.82 | 103.12±10.84 | 103.08± 10.83 | 0.811 |
| IMMEDIATELY AFTER | 84.96± 9.57 | 92.56±10.06 | 89.04±12.10 | **0.0467** |
| AFTER 5MIN | 78.32± 10.49 | 86.64±10.87 | 83.56±12.16 | **0.0347** |
| 10 MIN | 71.6± 10.19 | 85.48±10.27 | 86.64±13.74 | **<0.0001** |
| 15 MIN | 71.6± 8.80 | 85± 9.63 | 84.08±10.74 | **<0.0001** |
| 20 MIN | 75.8± 7.788 | 84.44± 9.44 | 87.2±10.94 | **0.00016** |
| 25 MIN | 78.92± 7.25 | 82.56± 9.97 | 87.72±9.68 | **0.004** |
| 30 MIN | 81.88± 8.27 | 82.44± 9.31 | 89.09±9.53 | **0.01** |
| 1 HR | 86.96± 10.24 | 84.84± 8.90 | 91.56±8.81 | 0.09 |
| 2 HR | 89.24± 10.53 | 86.86± 8.32 | 91±9.12 | 0.25 |
| 6 HR | 91± 9.99 | 88.72± 7.11 | 91.08±9.52 | 0.57 |
| 12 HR | 90.68± 8.89 | 90.08± 7.75 | 91.52±9.08 | 0.83 |
| 24 HR | 91± 8.68 | 90.68± 6.71 | 91.32±8.30 | 0.96 |
| 36 HR | 90.56±9.61 | 91.48± 6.70 | 93.24±8.35 | 0.51 |
| 48 HR | 93.44±9.70 | 91.8±6.33 | 93.72±8.70 | 0.68 |

As shown in table number 3, in Group D, mean pulse rate was 104.8 ± 9.82, in Group M mean pulse rate was 103.12 ± 10.84 and in Group P mean pulse rate was 103.08 ± 10.83 before starting of sedation which was found to be statistically insignificant (P .81). The mean pulse rate decreased after giving loading dose in all three groups. The mean pulse rate remained below base line throughout the sedation period in all three groups. The fall in mean pulse rate was more in dexmedetomidine group after loading dose which continued to be significant till 30 minutes of sedation as compared to midazolam and propofol group. The maximum fall in mean pulse rate was found at 15 minutes. After 30 minutes of sedation, the change in mean pulse rate was statistically insignificant when the three study groups were compared at the different time intervals.

**Table 4: Comparison of mean arterial pressure (map, mm hg) at different time interval (in MEAN ±SD)**

| TIME | GROUP D | GROUP M | GROUP P | p-Value |
|---|---|---|---|---|
| PRE SEDATION | 87.28±6.458 | 88.4±6.75 | 87.96±6.36 | 0.827 |
| IMMEDIATELY AFTER | 74.16±6.59 | 82± 7.20 | 80.24±7.76 | **0.0006** |
| AFTER 5MIN | 70.56±7.25 | 78.6±8.37 | 76.68±7.97 | **0.0015** |
| 10 MIN | 71.08±8.56 | 78.24±7.70 | 77.8±8.53 | **0.0043** |
| 15 MIN | 71.56±8.86 | 77.88±7.73 | 78.28±8.97 | **0.01** |
| 20 MIN | 72.92±8.26 | 77.76±8.3 | 78.96±7.8 | **0.025** |
| 25 MIN | 73.76±7.63 | 76.4±8.11 | 79±6.94 | 0.056 |
| 30 MIN | 74.68±7.52 | 76.4±7.58 | 79.68±6.7 | 0.054 |
| 1 HR | 76.2±7.32 | 79±7.78 | 80.48±6.35 | 0.108 |
| 2 HR | 77.76±6.99 | 80.4±7.43 | 81.48±6.33 | 0.156 |
| 6 HR | 78.8±6.42 | 80.76±7.09 | 81.52±6.53 | 0.169 |
| 12 HR | 78.8±5.78 | 81.36±6.80 | 82.12±5.63 | 0.138 |
| 24 HR | 79.52±6.16 | 81.12±6.76 | 81.88±5.65 | 0.331 |
| 36 HR | 79.16±5.8 | 77.68±17.1 | 83.24±5.3 | 0.181 |
| 48 HR | 80±5.84 | 81.84±5.6 | 82.4±4.88 | 0.232 |

As shown in table number 4, in Group D, mean arterial pressure was 87.28 ± 6.45, in Group M, mean arterial pressure was 88.4 ± 6.75 and in Group P mean arterial pressure was 87.96 ± 6.36 before starting of sedation which was found to be statistically insignificant (P= 0.827). Mean arterial pressure reduced in all three groups after giving the loading dose and remained below baseline throughout the 48 hour sedation period in all three groups. Fall in MAP was more in dexmedetomidine group after loading

dose which continued to be significant till 20 minutes of sedation as compared to midazolam and propofol group. After 20 minutes of sedation, the change in MAP was statistically insignificant when the three study groups were compared at the different time intervals.

**Total respiratory rate and Spo2 :** It was noted as total of patient's own rate plus ventilator rate. Respiratory rate was decreased in all the groups after sedation was started but respiratory depression was not found in any group. Mean respiratory rate remained above 18 in all three groups. $SpO_2$ remained above 97 % at all time intervals in all three groups. When the groups were compared at different time intervals, p value was more than 0.05 which was statistically insignificant for both RR and $SpO_2$.

**Table 5: Comparison of RASS at different time interval (in MEAN ± SD)**

| TIME | GROUP D | GROUP M | GROUP P | p-Value |
|---|---|---|---|---|
| PRE SEDATION | 1.92±0.57 | 2.08±0.27 | 2.08±0.4 | 0.325 |
| IMMEDIATLY AFTER | 0.52±0.50 | 0.72±0.45 | 0.56±0.5 | 0.319 |
| AFTER 5MIN | 0.12±0.33 | 0.24±0.59 | -0.08 ±0.57 | 0.091 |
| 10 MIN | -0.28±0.45 | -0.16 ±0.62 | -0.44 ±0.50 | 0.184 |
| 15 MIN | -0.96±0.73 | -0.68 ±0.62 | -1.08 ±0.4 | 0.06 |
| 20 MIN | -1.32±0.85 | -1.24 ±0.43 | -1.64 ±0.56 | 0.07 |
| 25 MIN | -1.52±0.77 | -1.56 ±0.50 | -1.84 ±0.47 | 0.127 |
| 30 MIN | -1.72±0.45 | -1.72 ±0.54 | -1.96 ±0.35 | 0.107 |
| 1 HR | -1.84±0.37 | -1.92 ±0.4 | -1.84 ±0.55 | 0.77 |
| 2 HR | -1.84±0.37 | -2±0 | -1.8±0.4 | 0.071 |
| 6 HR | -1.84±0.37 | -2.04 ±0.35 | -1.84 ±0.62 | 0.223 |
| 12 HR | -1.96±0.35 | -2.04 ±0.35 | -1.92 ±0.27 | 0.423 |
| 24 HR | -2.12±0.43 | -2.08 ±0.64 | -2.32 ±0.47 | 0.23 |
| 36 HR | -2.04±0.45 | -1.76 ±0.66 | -1.96±0.2 | 0.11 |
| 48 HR | -1.16±0.37 | -1.24 ±0.43 | -1.24 ±0.43 | 0.734 |

**Table 6: complications and interventions used to manage complications**

| Complication | Intervention | Group D | Group M | Group P |
|---|---|---|---|---|
| Bradycardia | Sedative drug dose reduction | 5 | 1 | 2 |
| | Atropine | 1 | Nil | Nil |
| Hypotension | Sedative drug dose reduction | 5 | 2 | 3 |
| | Iv fluids | 4 | 2 | 2 |

As shown in table number 5 and figure 1, RASS of 0 was attained immediately after loading dose in all three groups but deeper sedation level of RASS -2 was achieved at 15 minute in propofol group whereas it was achieved at 20 minutes in both dexmedetomidine and midazolam group. RASS remained in the target range of 0 to -2 in all the three groups throughout the sedation period. Whenever RASS reached above -2, dose reduction was done to maintain it between 0 to -2. As shown in table above, when the three groups were compared with respect to RASS maintained at different time intervals, the difference was found to be statistically insignificant ( $p > 0.05$) .

As shown in table 6,in group D, bradycardia was found in 6 patients out of 25, but only one patient required treatment with atropine whereas rest 5 patients required only sedative drug dose reduction. In group M bradycardia was found in 1 patient and in group P, bradycardia was found in 2 patients out of 25, but it was treated by sedative drug dose reduction in both group P and M and no patient required use of atropine.

In group D, hypotension was found in 5 patients and all of them were treated with IV fluids and dose reduction. In group M, hypotension was found in 2 patients and in group P, it was found in 3 patients. All were treated with drug dose reduction and IV fluids. None of the patients in any of groups required vasopressor. This showed that incidence of hypotension and bradycardia was more in dexmedetomidine group followed by propofol and then midazolam. None of the patients in all the groups showed the incidence of respiratory depression.

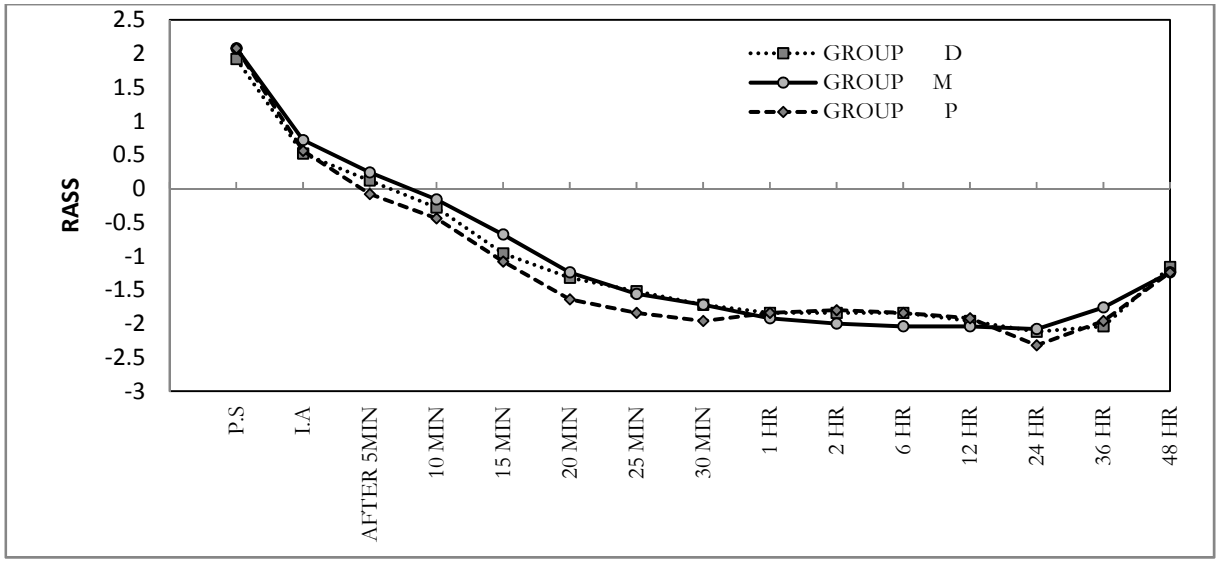


**Figure 1**: Comparison of RASS between patients on midazolam (M), propofol(P) and dexmedetomidine(D) sedative infusions, before starting of sedation, at 5 min interval after the loading dose till 30 minutes, then at 1st hour and 2nd hour, then at 6th hour and 12th hour and then every 12th hour till 48 hours.

## DISCUSSION

For the past decades, Gamma aminobutyric acid (GABA) receptor agonists (including propofol and benzodiazepine midazolam) have been the standard of care for sedation in the intensive care unit (ICU).[5] However, GABA-mimetic sedatives have significant limitations including delirium, respiratory depression, dependence and withdrawal.[6]

Midazolam has less active metabolites and faster elimination process but is of limited use because of the variability in duration of time for attaining consciousness after stopping the drug infusion in some patients. Propofol has a rapid distribution, metabolism and elimination process. But its prolonged infusions can lead to propofol infusion syndrome. Dexmedetomidine, a central and peripheral α2-receptor agonist distinct from GABA receptor for benzodiazepines and propofol, has been approved by the US Food and Drug Administration in mechanically ventilated patients.[7] It lacks suppression of the respiratory drive and does not depress the neurologic status, resulting in a state of cooperative sedation and preservation of neutrophil function. However, stimulation of the central Alpha 2 receptors can lead to bradycardia and hypotension especially in volume-depleted patients. Of note, its sympatholytic action can blunt the stress response in critically ill patients.

This study was intended to find a better ICU sedation protocol for ICU patients in our set up. We also intended to find effectiveness and potency of sedative property, haemodynamic stability and safety, and occurrence of any complication, of the three study drugs propofol, midazolam and dexmedetomidine, in mechanically ventilated patients in need of moderate sedation in ICU set up.

Our study showed that fall in mean pulse rate and mean arterial pressure was found in all three drugs after loading dose. The fall in mean PR and MAP was more in dexmedetomidine group after loading dose which continued to be significant till 30 and 25 minutes of sedation respectively as compared to midazolam and propofol group. After that, the change in mean PR and MAP was statistically insignificant when the three study groups were compared at the different time intervals. This also showed that the incidence of complications of hypotension and bradycardia was more in dexmedetomidine group patients. **Likewise, in 2012, Jakob SM et al [8]** found that dexmedetomidine patients had more hypotension and bradycardia as compared to propofol and midazolam. **In 2009, Riker RR, Shehabi Y, Bokesch PM, et al [9]** also found that the most notable adverse effect of dexmedetomidine was bradycardia.

**Jakob SM et al [8]** also reported that dexmedetomidine did not cause any respiratory depression and

midazolam and propofol also did not cause a significant decrease in RR in long term sedation. Similar results were obtained in our study also.

RASS remained in the target range of 0 to -2 in all the three groups throughout the sedation period of 48 hours by their infusion doses. Dexmedetomidine in the infusion dose range 0.4-0.5 ug/kg /hour was able to maintain the target RASS. Midazolam in the infusion dose range of 0.06 to 0.08 ug/kg/hour and propofol in the infusion dose range of 4-5 mg/kg/hour was able to maintain target RASS. In 2009, **Ruokonen E, et al**[10] found that in long term sedation, dexmedetomidine is comparable to propofol midazolam in maintaining sedation targets of RASS 0 to -3 but not suitable for deep sedation (RASS - 4 or less). Also the study by **Jakob SM et al**[8] concluded that dexmedetomidine was not inferior to midazolam and propofol in maintaining light to moderate sedation.

## CONCLUSION

It can be concluded that with dexmedetomidine similar levels of sedation can be achieved as compared to propofol and midazolam. All the three drugs- Midazolam, Propofol and Dexmedetomidine, caused fall in mean heart rate and mean arterial pressure but patients remained clinically stable. Fall was more with dexmedetomidine group but upto 30 minutes of sedation. Later on it was comparable to midazolam and propofol group. Dexmedetomidine group had more incidence of bradycardia and hypotension. All the three drugs maintained the respiratory parameters throughout the sedation period. Thus all the three drugs are equally efficacious and safe in regard to cardiorespiratory stability in maintaining target sedation in mechanically ventilated patients in ICU.

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