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Prospective Randomized Study to Compare Clonidine and Dexmedetomidine for Sedation in Mechanically Ventilated Patients

KEYWORDS: Sedation, Mechanical Ventilation, clonidine, dexmedetomidine

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ABSTRACT *BACKGROUND: This prospective, randomized study was undertaken to compare Clonidine and Dexmedetomidine for sedation in mechanically ventilated patients. Materials and Methods: The patients were divided into two groups. Group A (n=40) patients received dexmedetomidine infusion started as a loading dose of 0.7mcg/kg over a period of 10 mins followed by maintenance of 0.2 Mcg/kg/hr with dosage titration up to 0.7mcg/kg/hr. Group B (n=40) patients received clonidine infusion Sedation will be started with boluses in accordance with patient's body weight 1mcg/kg/hr of clonidine with titration being achieved up to 2mcg/kg/hr with dosage increments to achieve a score of 4 in SAS. The level of consciousness will be evaluated using Riker Sedation-Agitation Scale.*

RESULTS: More patients in Group A were found to achieve the target sedation level (Mean RSAS-4 and 80.67% patients) than Group B (Mean RSAS- 4.25, 70% patients). The heart rate was found to be significantly lower in Group B than in Group A from 14 hours to 48 hours. The decrease in heart rate was also higher in Group B than Group A. The baseline hemodynamic parameters were comparable in both groups. The Mean Arterial Pressure was found to be significantly lower in Group B than Group A from 14 hours to 48 hours of the study. Hypotension occurred in 2 of the 40 patients in Group A (5%) and 14 of the 40 patients in Group B (35%).

Conclusion: Dexmedetomidine is better drug in comparison to clonidine, as it provided better quality of sedation and hemodynamic stability.

INTRODUCTION

Patients undergoing mechanical ventilation experience pain, significant stress and neuro endocrine responses that increase oxygen consumption, trigger tachycardia and arrhythmias, cause electrolyte imbalances and initiate other potentially counterproductive physiologic reactions. The drugs most commonly used worldwide to produce sedation in ICU act mainly through GABA (Gamma Amino Butyric Acid) eg. Propofol and Benzodiazepines like Midazolam[1]. Later drugs like Opioids (Fentanyl, Remifentanil) [2,3]and alpha 2 agonists (Clonidine and Dexmedetomidine) came up. The opioid sparing sedatives, clonidine and dexmedetomidine (alpha2 agonist) with attenuated withdrawal symptoms led to resurgence in research of these agents. Clonidine[4] and Dexmedetomidine are thought to exert their sedative and hypnotic effects via the locus ceruleus. However recent clinical trials now permit an evidence-based approach to analgesia and sedation in critical care management. In this study, comparison has been taken on sedative, analgesic, cardio vascular effects and safety profile of Clonidine and Dexmedetomidine for patients requiring short term sedation in ICU.

MATERIAL AND METHOD

This study was conducted in National Institute Of Medical Sciences and Research medical college and hospital, Shobha nagar jaipur after its ethical committee approval critically ill patients, patients of both sexes, age group 15 – 70 years of different etiological groups- COPD, sepsis and post-surgical states, requiring mechanical ventilation (MV) for 24 hrs or more and in need of sedation, were studied in a prospective, randomized pattern .Patients of known allergy to drugs used in sedation protocol (clonidine, dexmedetomidine, midazolam), Pregnant patients, Patients with secondary exclusion criteria: complications necessitating termination of sedation, transferral or death (within 24 hrs), Patients with neurological condition, Haemodynamically unstable patients were exluded from the study. Prior to admission to ICU, physical examination, baseline vitals, ECG, Temperature and CVP were noted. Hematological and biochemical profile were obtained prior to administration of sedatives and 24 hours after the study period. Optimum ABG levels were obtained. The following information were collected and recorded, Patient particulars, Cause of intubation, Choice of sedation, Total dose of sedatives, Duration of MV and sedative infusion, Occurrence of ventilator associated pneumonia. The patients were divided into two groups. Group A- patients receivied dexmedetomidine infusion started as a loading dose of 0.7mcg/kg over a period of 10 mins followed by maintenance of 0.2 Mcg/kg/hr with dosage titration up to 0.7mcg/kg/hr. Group B - patients receivied clonidine infusion Sedation will be started with boluses in accordance with patient's body weight 1mcg/kg/hr of clonidine with titration being achieved up to 2mcg/kg/hr with dosage increments to achieve a score of 4 in SAS. The level of consciousness will be evaluated using Riker Sedation-Agitation Scale (RSAS) where 1=Unarousable (Minimal or no response to noxious stimuli, does not communicate or follow Commands), 2 = Very Sedated (Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously), 3 = Sedated (Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again,follows simple commands), 4 = Calm and Co operative (Calm, awak-

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ens easily, follows commands), 5 = Agitated (Anxious or mildly agitated, attempting to sit up, calms down to verbal instructions), 6 = Very Agitated (Does not calm down despite frequent verbal reminding of limits, requires physical restraints, biting ETT), 7 = Dangerous Agitation (Pulling at endotracheal tube (ETT), trying to remove catheters, climbing over bedrail, striking at staff, thrashing side-to-side). The assessment would be obtained on arrival in the ICU, 10 and 30 minutes after the commencement of the infusion and 2 hourly thereafter for the study period for the first day and 12 hourly as needed until extubation or for maximum allowable time. Riker SAS Score of 4 was considered as target sedation and drugs were accordingly titrated. Rescue sedation with i/v midazolam bolus of 0.1mg/kg was given if the patient did not achieve target sedation on titrating the sedative to the maximum selected dose (2mcg/kg/hr for clonidine and 0.7mcg/kg/hr for dexmedetomidine) or if the patient experienced side effects, i.e., Hypotension(MAP<60 mm Hg or blood pressure fall >20 % fall from baseline). A weaning trial was given after 24 hours and if weaning was not possible, sedation was resumed.

Continuous data were summarized as Mean ± SD while discrete (categorical) in %. The outcome measures of the two groups over the periods were compared by repeated measures two factor (Groups and Periods) analysis of variance (ANOVA) using general linear models (GLM) followed by Newman-Keuls post hoc test. Groups were also compared by independent Student's t test. The categorical variables were compared by chi-square ($\chi 2$) test. A two-sided (α=2) $p<0.05$ was considered statistically significant.

RESULTS

Over a period of 12 months, 80 patients were enrolled in the study to receive sedation with either dexmedetomidine (n = 40) or clonidine (n = 40). These included 57 post-surgical, 06 Blunt Injury Chest and Abdomen, 05 Firearm injuries, 03 COPD, 02 Poly trauma, 01 Snake Bite and 06 other miscellaneous medical conditions evenly distributed in each group. Demographic data, APACHEII scoring, Biochemical, Hematological and Arterial blood gas analysis done at admission as well as at 24 hours were found to be comparable. [**TABLE 1]** Riker sedation agitation score was found to be significantly ($p<0.05$) higher from 14th hour of sedation till 36th hour of sedation in Group B than Group A with a spike in sedation agitation score (mean score- 5) being observed in the 18th hour till 20th hour of sedation. In Group A, 80.6% observations on Riker Sedation Agitation Scale, were in the target sedation range (RSAS- 4) while in Group B, 70.34% observations were in the target sedation range (RSAS: 4) [**Fig. 1]**. The heart rate was observed to be similar from admission to 12 hours in both the groups ($p>0.05$). The heart rate was then found to be significantly ($p<0.05$) lower in Group B than Group A from 14 hours to 48 hours. Bradycardia occurred in 2 of the 40 patients in Group A and 12 of the 40 patients in Group B (P = 0.01) **[Fig.2]**. The baseline hemodynamic parameters were comparable in both groups. The MAP was observed to be similar from 10 minutes to 12 hours in both the groups ($p>0.05$). The Mean Arterial Pressure was then found to be significantly ($p<0.05$) lower in Group B than Group A from 14 hours to 48 hours. Hypotension occurred in 2 of the 40 patients in Group A (5%) and 12 of the 40 patients in Group B (35%) (P = 0.01) [**Fig.3]**.The mean ± SD maintenance infusion dose was 31.59±8.69 mcg/kg/h for dexmedetomidine and 112.19±19.14 for clonidine, Since there is no equipotent dosage of these drugs for sedation, hence a comparison can't be made. Rescue sedation with Midazolam was needed by 14 patients in dexmedetomidine administered and by 23 patients in clonidine administered patients (P = 0.01) to achieve the target sedation level. The mean number of times rescue sedation was required was significantly more in Group B (4.17±1.5 times) than in Group A (2±0.78 times) (p value-0.01). Mean time for extubation was similar in both groups, being 28.11 h (range: 20-48 h) in Group A patients and 26.93 h (range: 12-48 h) in Group B. There were no adverse respiratory events after extubation in any patient in either group. Mean Duration of stay in ICU after the start of sedation were found to be comparable. [**TABLE 1]**

DISCUSSION

Sedation practices have been used since a long time to comfort the patient from the effects of mechanical ventilation and various intensive care unit procedures which can result in pain, significant stress and neuro endocrine responses that increase oxygen consumption, trigger tachycardia and arrhythmias, these can be ameliorated by providing adequate sedation and analgesia titrated to discernible and clinical end points. Current Pain, agitation and delirium guidelines5 endorse a benzodiazepine sparing approach to aid in achieving optimal patient outcomes.

The demographic variables in two groups viz Age, Gender, APACHE II Scores and the types of patients taken in the study were comparable and did not show any statistically significant difference. This study and many previous studies[6, 8, 9, 10] have documented dexmedetomidine to be a safe and effective agent for ICU sedation of patients in need of mechanical ventilation.

Percentage of patients who attained target sedation was significantly higher in Group A compared with Group B (80.67% vs. 70.3% in Groups A and B, respectively, P = 0.03). Our findings on dexmedetomidine treated patients is in concurrence with previous studies[6, 7, 10] such as that in Venn RM et al and Srivastav U et al where the percentage of Dexmedetomidine patients in taget sedation range were 86%. However, our findings are in contrast with those of Riker et al[7] who suggested that dexmedetomidine attained target sedation less frequently. They had recruited only medical patients, while our patients were postsurgical, of poly trauma and of various medical conditions. This may possibly be the cause of discrepancy. Dexmedetomidine is 8 times more specific for alpha2 receptors than clonidine and the improved specificity for the alpha2 adrenoreceptors, especially for the 2A subtype may make it to be a much more effective sedative than clonidine[11].

In general, hemodynamic stability was preserved in most patients receiving dexmedetomidine, a finding in agreement with many previous studies.[6 ,8,10] Hypotension occurred in 2 of the 40 patients in Group A (5%) and 12 of the 40 patients in Group B (30%) (P = 0.01). 12 patients in Group B requiring rescue sedation to achieve target sedation experienced hypotension on increasing the dose from 1 up to 2 mcg/kg/h. This observation was consistent with previous studies of clonidine where adverse hemodynamic effects occurred at doses required for sedation1[2, 13]. Previous studies of ICU sedation[8,10] with dexmedetomidine have found no or minimal increase in heart rate and BP following abrupt cessation, the finding similar to this study. As many studies have stated that abrupt discontinuation of the Clonidine[10,14,12] results in rebound hypertension, so we reduced the doses gradually before weaning off the patient from mechanical ventilation.

Since, there is no evidence based equipotent dose of Dex-

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medetomidine and Clonidine for sedation in ICU, hence their doses cannot be compared. In a retrospective analysis of patients receiving clonidine for ICU sedation, Gillison et al[14] have reported that clonidine reduces requirement of rescue sedation and analgesia, but at the cost of higher than routinely prescribed dose. Wan et al15[5]and Esmaoglu et al[16] observed that Dexmedetomidine usage helps to shorten the duration of MV.

Srivastav U et al[10] observed hypotension more commonly in Clonidine treated patients (11/35) in comparison to Dexmedetomidine Group (3/35). Since, our study lasted for only 48 hours, there was no ventilator associated pneumonia or any case of delirium.

CONCLUSION

Riker sedation agitation score was almost constant across the time intervals in both the groups. More patients in Group A were found to achieve the target sedation level than Group B. The heart rate was observed to be similar from baseline to 12 hours in both the groups. The heart rate was then found to be significantly lower in Group B than in Group A from 14 hours to 48 hours. Hemodynamic parameters were comparable in both groups. The MAP was observed to be similar from 10 minutes to 12 hours in both the groups. The Mean Arterial Pressure was found to be significantly lower in Group B than Group A from 14 hours to 48 hours of the study. Dexmedetomidine is better drug in comparison to clonidine, as it provided better quality of sedation and hemodynamic stability.

Table-1:Basic characteristics of the patients

	Group A (n=40)	Group B (n=40)	p-value
Age (in years), mean±SD	37.58±14.24	37.90±15.40	0.92
Gender			
Male, no. (%)	22 (55.0)	23 (57.5)	0.82
Female, no. (%)	18 (45.0)	17 (42.5)	
APACHE II	14.95±3.43(10-24)	15.05±4.58(10-24)	0.93
Temperature	100.633±1.76	100.52±1.73	0.77
Central venous pressure	9.7±1.98	10.43±1.74	0.09
ICU stay after start of sedation(in days)	5.18±6.76	4.02±4.91	0.38
Mean extubation time(in hours)	28.11±10.01	20.93±12.69	0.45
Mean dose	31.59±8.69 mcg	112.19±19.14 mcg	-
Number of times rescue sedation required	2±0.78	4.17±1.5	0.01

*P <0.05 significant

Table 2: Various blood parameters on admission

Characteristics	Group A	Group B	p value
Hb(in gm%)	10.03±1.93	10.70±1.47	0.08
TLC(x1000/ mm3)	9.65±1.73	9.83±1.5	0.63
Sr.creatinine	1.38±1.11	1.1±0.11	0.12
P/F RATIO	220.13±143.18	243.6±128.11	0.44
Parameters 24 hours after admission:			
Hb(in gm%)	10.65±1.46	10.73±1.71	0.83
TLC(x1000/ mm3)	10.43±1.53	10.35±1.66	0.83
Serum creatinine	0.94±0.27	0.94±0.16	0.95
P/F RATIO	192.4±129.12	218.50±130.65	0.37

*P<0.05=significant

Fig. 1: Comparison of Riker sedation agitation scale across the time intervals among the groups:

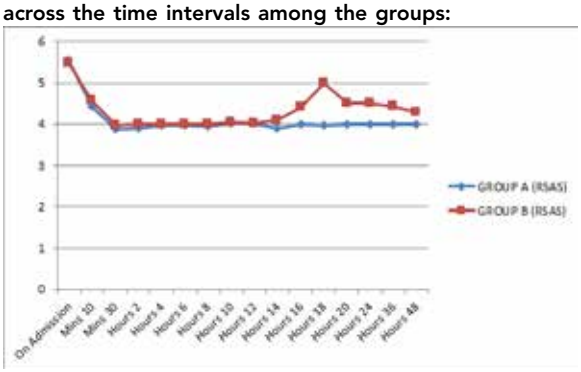


Fig. 2: Comparison of heart rate across the time intervals among the groups

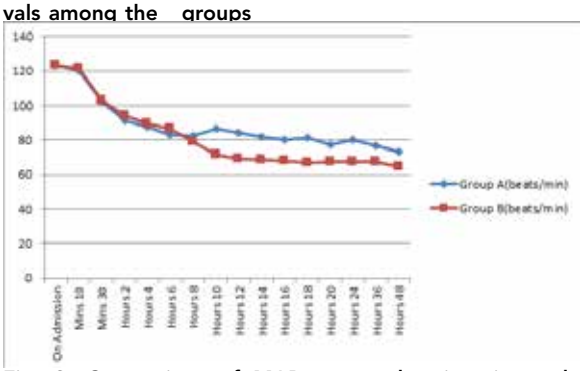
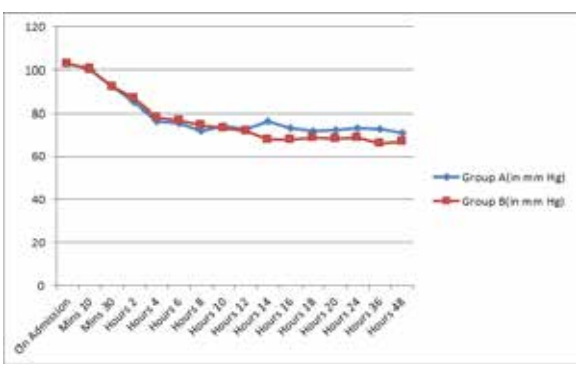


Fig. 3: Comparison of MAP across the time intervals amongthegroups



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