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A STUDY TO COMPARE THE EFFICACY OF DEXMEDETOMIDINE AND MIDAZOLAM FOR SEDATION IN CRITICALLY ILL PATIENTS IN INTENSIVE CARE UNIT.

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ABSTRACT

Background: Sedation forms an integral part of management of critically ill patients in ICU. Sedatives are used routinely in all ICU's throughout the world. For decades, Gama aminobutyric acid (GABA) receptor agonists (including propofol and benzodiazepines such as midazolam) were used as sedative drugs for ICU patients Worldwide. Dexmedetomidine is an alpha-2A adrenoreceptor agonist, providing sedation and anxiolysis. In addition to sedation, dexmedetomidine provides analgesic effects, a lack of respiratory depression and may establish a more natural sleep-like state. Midazolam is selected as comparator owing to its frequent use in ICU for sedation.

Materials & Methods: A prospective, double blinded, randomized trial was conducted in ICU of McGann hospital after taking permission from Institutional Ethical Committee. Study was done in 60 patients. They were randomly allocated into two groups. **Group D – Dexmedetomidine (n=30)** received Loading dose: 1microgm/kg Maintenance dose: 0.4microgm/kg/hr. **Group M – Midazolam (n=30)** Loading dose: 0.05mg/kg, Maintenance dose: 0.06mg/kg/hr. Hemodynamic variables, Richmond Agitation and Sedation Scale (RASS) were recorded. All data were represented as mean± SD. Statistical analysis was done with SPSS version 21.0.

Results : Hemodynamic variables & sedation scores were better in Group D than in group M & were statistically significant. There were no major adverse effects in both the groups.

Conclusion: This study (which incorporated best sedation practices including a light-to- moderate sedation level and daily arousal assessments in both study groups) showed no difference in the time patients spent within the target sedation, however dexmedetomidine has provided better hemodynamic stability and reduced development of delirium and also cause resolution of delirium

KEYWORDS :

INTRODUCTION

Sedation forms an integral part of management of critically ill patients in ICU. Sedatives are used routinely in all ICU's throughout the world. The consequences of inadequate sedation and analgesia can be substantial, including self-removal of important intraluminal tubes and vascular catheters, aggressive behaviour by patients against care providers and poor patient–ventilator synchrony.[1] For decades, Gama aminobutyric acid (GABA) receptor agonists (including propofol and benzodiazepines such as midazolam) were used as sedative drugs for ICU patients Worldwide.[2,3,4] These medications provide adequate sedation but also can cause over sedation and respiratory depression which can lead to prolonged duration of mechanical ventilation, longer ICU and hospital stays, and inability of patients to communicate with health care providers or family members.[3] Dexmedetomidine is an alpha-2A adrenoreceptor agonist, providing sedation and anxiolysis via receptors within the locus ceruleus, analgesia via receptors in the spinal cord, and attenuation of the stress response with no significant respiratory depression. In addition to sedation, dexmedetomidine provides analgesic effects, a lack of respiratory depression and may establish a more natural sleep-like state. Midazolam is selected as comparator owing to its frequent use in ICU for sedation.[6-12]

AIMS AND OBJECTIVE

1. To compare the efficacy of Dexmedetomidine and Midazolam for sedation in ICU.
2. To study safety of both the drugs in terms of Hemodynamic variables (HR, BP, O_2saturation).
3. To watch for any adverse events related to study drug.

MATERIALS AND METHODS

This prospective, double blinded, randomized trial was conducted in ICU after taking permission from Institutional Ethical Committee. Written informed consent was taken from patients' legally authorized representatives. Study was conducted in 60 patients from January 2017 to December 2017.

Inclusion criteria:

- Patients aged between 18 years & 60 years.
- intubated and mechanically ventilated for less than 48 hours prior to start of study drug.
- anticipated ventilation and sedation duration of at least 2 more days.

Exclusion criteria:

- trauma or burns, dialysis of all types, pregnancy or lactation
- neuromuscular blockade other than for intubation, epidural or spinal analgesia,
- general anesthesia 24 hours prior to or planned after the start of study drug infusion.
- unstable angina or acute myocardial infarction, left ventricular ejection fraction less than 30%, heart rate less than 50/min, second- or third-degree heart block,
- systolic blood pressure less than 90 mm Hg despite continuous infusions of 2 vasopressors before the start of study drug infusion.
- Patients with renal insufficiency were randomized and treated; however, patients were discontinued if they required dialysis.

After taking detailed information regarding severity of illness, sedative and analgesic therapy prior to initiation of study, each patient received study drug within 48 hours after intubation. Other sedative agents were discontinued prior to the initiation of study drug, and patients were required to be within the Richmond Agitation and Sedation Scale (RASS) target range.

Patients are randomly allocated into 2 groups

Group D – Dexmedetomidine (n=30)
Loading dose: 1microgm/kg
Maintenance dose: 0.4microgm/kg/hr.

Group M – Midazolam (n=30)
Loading dose: 0.05mg/kg
Maintenance dose: 0.06mg/kg/hr.

Dosing of study drug was adjusted by the managing clinical team based on sedation assessment performed with the RASS score

Richmond Agitation and Sedation Scale:

+4 Combative Overtly combative, violent, immediate danger to staff
+3 Very agitated pulls or removes tubes or catheters
+2 Agitated frequent no purposeful movements, fights ventilator
+1 Restless anxious but movements not aggressive vigorous
0 Alert and calm
-1 Drowsy Not fully alert, but has sustained awakening (eye opening / eye contact) to voice (>10 seconds)
-2 Light sedation Briefly awakens with eye contact to voice (<10 seconds)
-3 Moderate sedation Movement or eye opening to voice (but no eye contact)
-4 Deep sedation No response to voice, but movement or eye opening
-5 Unarousable No response to voice or physical stimulation

Patients not achieving target sedation range in either group were given open-label midazolam bolus doses of 0.01 to 0.05 mg/kg at 10- to 15-minute intervals until adequate sedation (RASS range, −2 to +1) was achieved. Maximum dose is 4 mg in 8 hours.

- If over sedation (RASS range, −3 to −5) occurs it responds to decreasing study drug infusion rate or temporary stopping the infusion.
- Intravenous haloperidol, in increments of 1 to 5 mg was used for treatment of agitation or delirium, repeated every 10 to 20 minutes as needed.
- Analgesia with fentanyl bolus doses (1.0 µg/kg0 were given every 15 minutes. Intravenous bolus doses of fentanyl could also be given prior to an anticipated noxious stimulation such as chest physiotherapy or suctioning. Fentanyl patches were not permitted.
- No other sedatives or analgesics were allowed

Outcome Measures and Safety End Points

- The primary end point was the percentage of time within the target sedation range (RASS score −2 to +1) during the treatment period.
- Secondary end points included prevalence and duration of delirium, use of fentanyl and open-label midazolam, hemodynamic stability.
- patients within the RASS range of −2 to +1 were asked to perform 4 tasks open eyes to voice command, track investigator with eyes, squeeze hand stick out tongue

Patients were considered awake with successful completion of the assessment when they could perform 3 of 4 tasks Vital signs were recorded a minimum of every 2 hours, with every change of study drug dose, and at the time of intervention for adverse events. The protocol prespecified that blood pressure and heart rate values were considered adverse events if systolic blood pressure was less than 80 or greater than 180 mm Hg, diastolic blood pressure was less than 50 or greater than 100 mm Hg, or heart rate was less than 40/min or greater than 120/min. Interventions for bradycardia, tachycardia, and hypertension included titration or interruption of study drug or administration of medication; interventions for hypotension included titration or interruption of study drug, intravenous fluid bolus, or drug therapy.

Statistical Analysis &Sample Size Determination.

Our objectives were to compare safety and efficacy during exposure to dexmedetomidine sedation in ICU, so in sample size determination we considered drug exposure, efficacy, and safety parameters.

For the primary efficacy variable, the mean percentage of time within target sedation range was estimated to be 85% for dexmedetomidine and 77% for midazolam, based on a previous pilot study.[34] It was anticipated that 60% of patients would remain intubated for 72 hours after randomization. A minimum of 30 dexmedetomidine-treated patients exposed for at least 12 hours would allow adverse events occurring in 10% of the dexmedetomidine group to be estimated with a 95% confidence interval (CI) ±5%.

An estimated 100 dexmedetomidine-treated patients were expected to remain intubated for at least 12 hours. Considering each of these requirements, enrollment of 60 patients randomized to receive dexmedetomidine and midazolam would have 96% power at an α of .05 to detect a 7.4% difference in efficacy for the primary outcome.

Efficacy and Safety Analysis.

The primary efficacy and safety analyses were conducted on all randomized patients receiving any dose of study drug. The primary efficacy analysis (percentage of time within the target sedation range during the double-blind treatment period) was calculated by t/T*100%

Where, t = total time that the patients remained within the target RASS range

T = amount of time the patient remained in the double-blind treatment period

The mean difference and 95% CI between the dexmedetomidine and midazolam treatment groups were calculated and compared between treatment groups with Student's t test.

OBSERVATIONS & RESULTS

This study was conducted to compare efficacy of Dexmedetomidine and Midazolam in terms of level of sedation and hemodynamic variables (HR, BP, SpO2) for 12 hours. A total of 60 eligible patients were randomized in two groups. The baseline demographic variables like age, sex, weight was comparable in both the groups.

Table 1 Demographic data

		Group D (n=30)	Group M (n=30)
Age in year		43.96 ± 14.72	45.02±11.36
Sex	Male	16	17
	Female	14	13
Weight in kg		58.66 ±7.28	57.44 ± 9.54

Table 2: Heart Rate Mean & Standard Deviation

Time	Dexmedetomidine (n=30)		Midazolam (n=30)	
	Mean HR	SD	Mean HR	SD
0 min	94.43	14.59	95.66	18.52
5 min	86.33	15.45	88.90	17.46
10min	80.03	13.81	85.56	15.96
15 min	73.33	13.14	86.44	14.68
30 min	68.77	12.33	85.53	14.18
1 hour	67.63	11.01	83.46	12.88
2 hours	67.10	9.11	80.76	15.30
4 hours	64.77	10.59	80.63	12.55
6 hours	66.50	9.25	85.16	13.70
8 hours	6633	7.26	84.86	12.89
10 hours	63.97	6.94	84.00	12.33
12 hours	62.23	7.08	82.00	11.87

Figure 3 Comparison of Heart Rate among group 1 and 2 at different time intervals

Time	Dexmedetomidine (n=30)		Midazolam (n=30)	
	Mean Systolic BP	SD	Mean Systolic BP	SD
0 min	125.83	10.36	129.00	9.54
5 min	119.61	10.14	121.60	9.27
10min	107.43	14.81	118.76	8.44
15 min	100.07	12.11	113.53	8.52
30 min	101.67	11.20	110.43	7.67
1 hour	98.37	9.95	108.26	8.33
2 hours	94.80	12.31	104.93	8.68
4 hours	93.03	9.32	105.00	6.82
6 hours	92.50	8.80	104.80	6.54
8 hours	95.43	10.01	104.93	9.86
10 hours	98.83	8.25	107.53	8.03
12 hours	99.63	8.59	109.86	6.30

In Dexmedetomidine treated patients mean systolic BP remains lower than midazolam group at any point of time during sedation. But the difference is statistically not significant at 95% confidence interval (p>0.05), baseline systolic BP were comparable in both the groups

In Dexmedetomidine treated patients mean diastolic BP remains lower than midazolam group at any point of time during sedation.

But the difference is statistically not significant at 95% confidence interval (p>0.05), baseline diastolic BP were comparable in both the groups

Other Sedative/Analgesic Medication Delivery

Table 5 - % of patients requiring additional drugs for sedation

	Dexmedetomidine	Midazolam
Open label Midazolam Bolus	13.33	10
Fentanyl bolus for analgesia	10	20

The mean maintenance infusion dose was 0.23 µg/kg / hour for dexmedetomidine and 0.056 mg/kg / hour for midazolam.

Open-label midazolam was administered to more dexmedetomidine-treated patients (4/30[13.3%] vs 3/30[10%]) but the difference was statistically insignificant (P = .69) The median open-label midazolam dose was similar. The percentage of patients requiring fentanyl was similar, as was the median fentanyl dose during the double-blind period

Delirium and nursing assessments
The prevalence of delirium just before starting study drug was similar between treatment groups. The prevalence of delirium was 13.33% (4 out of 30 patients) in dexmedetomidine-treated patients vs 36.66% (11 out of 30 patients)in midazolam-treated patients (23.33% difference; 95% CI; P < .05)

Safety
All-cause 30-day mortality from ICU admission was not different between treatment groups, and no death was considered related to study drug.

More dexmedetomidine-treated patients developed adverse events related to treatment (3.33% vs 1.94%; P <0.05), primarily due to a greater incidence of bradycardia (4.17% vs 0.27% ; p=0.04) (Table 3). This included heart rates less than 50/ min (occurring in 6 dexmedetomidine-treated patients) who required an intervention for bradycardia that included titration of study drug infusion and use of atropine. Among midazolam-treated patients, 1 received atropine for bradycardia.

A higher incidence of tachycardia in midazolam group(5 patients in midazolam group vs 1 patient in dexmedetomidine group)and more hypertension requiring treatment was noted in the midazolam-treated patients

Table 6 Values are % of adverse events

	Dexmedetomidine	Midazolam
Tachycardia	0	2.50
Bradycardia	4.17	0.27
Hypertension	0.55	1.11
Hypotension	5.00	1.90

DISCUSSION

Providing sedation for patient comfort is an integral component of bedside care for nearly every patient in the intensive care unit (ICU). For decades, γ-aminobutyric acid (GABA) receptor agonists (including propofol and benzodiazepines such as midazolam) have been the most commonly administered sedative drugs for ICU patients worldwide.[2,3,4,5] Dexmedetomidine is an α-2 adrenoreceptor agonist with a unique mechanism of action, providing sedation and anxiolysis via receptors within the locus ceruleus, analgesia via receptors in the spinal cord, and attenuation of the stress response without any significant respiratory depression.[21,22]We hypothesized that a sedation strategy using dexmedetomidine would result in improved outcomes in mechanically ventilated, critically ill medical and surgical ICU patients compared with the standard GABA agonist midazolam. To test this hypothesis, we randomized patients in 2 groups to receive dexmedetomidine or standard sedation using midazolam infusions for up to 12 hours of mechanical ventilation. Efficacy analysis: The primary outcome for this study that is % of time within the target sedation range, was not different between patients treated with dexmedetomidine or midazolam, exceeding 75% with both medications.(Table 5, Figure5)In previous study of Pandharipande PP, Pun BT, Herr DL, et al suggested that dexmedetomidine attained the sedation target more frequently.[12] In study of Ely EW, Jonuye SK, Bernard GR et al also concluded that dexmedetomidine treated patients remained in target sedation range for greater percentage of time. This difference can be explained by our study design, which incorporated new standard elements for ICU sedation practice, including a light-to- moderate sedation target (RASS score −2 to +1), delirium assessment, and study drug titration. In the context of recently published study of Girard TD, Kress JP, Fuchs BD, et al comparing dexmedetomidine with propofol, suggest that α-2 agonists improve many important aspects of critical care, namely, less delirium and shorter duration of ventilator stay.[8]Hemodynamic stability and safety: We have observed that there is reduction in heart rate among both the groups after starting infusion. (Table 2,3,4 Figure 2,3,4) Despite the similar levels of sedation attained by patients treated with dexmedetomidine and midazolam, several important differences were noted in this prospective, double-blind, randomized study. There is greater hemodynamic stability in dexmedetomidine treated patients as compare to midazolam group. The incidence of tachycardia and hypertension was more in midazolam group at different time intervals. This difference is statistically more significant at p value < 0.05. Bradycardia was more common among dexmedetomidine-treated patients. In a study of Riker RR, Fraser GL et al who compared the sedation and adverse events of dexmedetomidine and midazolam also had similar results. They claimed sympatholytic effect of dexmedetomidine for the above mentioned results and suggested use of dexmedetomidine for blunting stress response of intubation.[10] Delirium: Each additional day of delirium increases the risk of prolonged hospitalization by 20% and increases the likelihood of a poor functional status at 3 and 6 months.[36,37] Jackson JC, Gordon SM, Girard TD, et al concluded that Dexmedetomidine appears to be the first drug to both reduce the development of delirium and to cause resolution of delirium if it develops in the ICU.[38] Maldonado J, Wysong A, van der Starre P et al concluded that Dexmedetomidine binds at α_2 receptors rather than GABA receptors; this may explain the improved outcomes in terms of reduced incidence of delirium.[13] Additional sedative/analgesic medication: Open-label midazolam was administered to more dexmedetomidine- treated patients (4/30 [13.33%] vs 3/30 [30%]; P = .02). The median open-label midazolam dose was similar. The percentage of patients requiring fentanyl for analgesia was similar,(3/30[10%] vs 6/30[20%] p> 0.05) as was the median fentanyl dose during the double-blind period (Table 6). Shehabi Y, Grant P, Wolfenden H et al used morphine boluses for rescue sedation and analgesia and found similar results.[24] Drugs like propofol , lorazapam can be used as additional sedative agents but our study design doesn't include them. Additional Benefits: In addition to sedation, dexmedetomidine provides analgesic effects, a lack of respiratory depression, sympatholytic blunting of the stress response, preservation of neutrophil function (compared with the neutrophil-suppressing effect of GABA-agonist medications), and establish a more natural sleep-like state.[28,32]

Limitations of this study:
Midazolam was selected as the comparator medication owing to its frequent use for long-term sedation. Although midazolam is often identified as the sedative most commonly used for long-term sedation[2,5,17] common alternatives such as lorazepam or propofol were not tested in this study as our study design doesn't support it.

We have provided sedation for a limited duration(12 hours). Thisstudy cannot evaluate the efficacy of dexmedetomidine for long term sedation.

Riker RR, Ramsay MAE et al administered these sedative agents until extubation and concluded that dexmedetomidine treated patients are extubated early. It decreases the duration of ICU stay.[34]

The impact of study drug on length of ICU stay and duration of extubation cannot be assessed correctly from our study. Shehabi Y, Ruettimann U et al suggested that length of ICU stay decreased by 3.7 days with prolonged Dexmedetomidine sedation.[39]

We excluded patients requiring renal replacement therapy to avoid the confounding effect of accumulating midazolam metabolites and dialysis clearance of medication.

De Wolf AM, Fragen RJ et al Analysed dexmedetomidine and midazolam use in patients with renal dysfunction and concluded that the effect of both drugs is prolonged.[40,41]

SUMMARY & CONCLUSION

This study (which incorporated best sedation practices including a light-to- moderate sedation level and daily arousal assessments in both study groups) showed no difference in the time patients spent within the target sedation, However dexmedetomidine has provided better heamodynamic stability and reduced development of delirium and also cause resolution of delirium

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