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A Study to Assess the Effect of Dexmedetomidine versus Midazolam for Sedation of Critically Ill Patients

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Background: Sedation is a common practice in ICU in order to reduce the anxiety, increase tolerance and to improve the outcomes of intervention is the Intensive care Unit. This is due to patients admitted to the ICU require invasive and uncomfortable interventions such as mechanical ventilation. The sedation of the patient reduces the stress response, provides anxiolysis, improves the tolerance of ventilator support and facilitates nursing care. *Objective:* To compare the effect of Dexmedetomidine versus Midazolam for sedation of critically ill patients. *Materials and Methods:* A prospective, randomized, double blinded study was undertaken in the Department of Emergency Medicine, of Chigateri General Hospital and Bapuji Hospitals attached to JJM Medical College, Davanagere from March 2012 to March 2013. A total of 100 patients aged above 18 years who were critically ill and admitted to Intensive care units of the above hospitals were included as subjects. *Results:* The mean age of the subjects of Dexmedetomidine group was 41.9 (±12.4) years and patients of midazolam group was 41.1 years.The mean weight of the patients in Dexmedetomidine group was 57.2 (±13.5) kgs and the mean weight of the patients in Midazolam group was 57.8 (±12.2) Kgs.The mean sedation score was 0.6 in dexmedetomidine group and 0.1 in Midazolam group at 5 mins after admission. *Conclusion:* This study had shown the efficacy of Dexmedetomidine as equal as Midazolam. The hemodynamic parameters also remained normal while use of this drug. This study had also shown that the less adverse effects and number of add on sedative agents were less in Dexmedetomidine group compared to midazolam.

Keywords: Sedation; Midazolam; Dexmedetomidine; Criticalill.

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Introduction

Sedation is a common practice in ICU in order to reduce the anxiety, increase tolerance and to improve the outcomes of intervention in the Intensive care Unit. This is due to patients admitted to the ICU require invasive and uncomfortable interventions such as mechanical ventilation [1]. The presence of endotracheal tube, the performance of various diagnostic tests and interventions such as tracheal suctioning, mobilization and transportation may necessitate either intermittent or continuous administration of sedative drugs [2].

The sedation of the patient reduces the stress response, provides anxiolysis, improves the tolerance of ventilator support and facilitates nursing care

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[3-5]. But the sedatives have adverse effects and have potential to prolong the mechanical ventilation and also increases the health care costs. An ideal sedative agent should have action which is rapid in onset, should be effective at providing adequate sedation, allow rapid recovery after discontinuation, be easy to administer, lack drug accumulation, have a few adverse effects, interact minimally with other drugs and should be inexpensive [6]. The consequences of inadequate sedation and analgesia can be substantial, including self removal of important intralumenal tubes and vascular catheters, aggressive behavior by patients against care providers,and poor patient–ventilator synchrony [7].

Several sedatives were used to prevent the agitation of critically ill patients in Intensive Care Unit. 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 [8]. These medications provide adequate sedation but also can cause over sedation. Over sedation and its side effects can lead to prolonged duration of mechanical ventilation, longer ICU and hospital stays, increased incidence of ventilator-associated pneumonia, and inability of patients to communicate with health care providers or family members [9].

Currently available sedatives are problematic in long term sedation. Benzodiapines and propofol are incriminated to accumulate in the body. High dose and prolonged use of propofol have been found to results in prolonged infusion syndrome [10].

Midazolam is a potent imidiazobenzodiazepine which possesses typical benzodiazepine properties namely hypnotic, amnestic, anticonsulvant and anxiolytic activity. The benzodiazepine, midazolam, has become the most frequently used medication given for sedation. Midazolam has a number of beneficial effects when used for sedation, fast onset and limited duration of action. Despite having a number of beneficial effects, it is far from an ideal agent having untoward side effects such as restlessness, paradoxical reaction, cognitive impairment, amnesia and respiratory depression [11].

Now newer drugs are being used for sedation in critically ill patients which have benefits over the conventional drugs. Dexmedetomidine is an α_{2a}adrenoreceptor agonist with a unique mechanism of action, providing sedation and anxiolysis via receptors within the locus ceruleus, a small nucleus present in the pons, 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, sympatholytic blunting of the stress response, preservation of neutrophil function (compared with the neutrophil-suppressing effect of GABA agonist medications), and may establish a more natural sleep-like state [8].

Since the dexmedetomidine is new drug, fewer studies have been conducted so far in India and the World. The dexmedetomidine as sedative especially in intensive care unit has not been explored by the studies. Hence, the present randomized single blinded study was undertaken in a manner to evaluate the onset time, duration and quality of sedation with dexmedetomidine compared to midazolam in critically ill patients.

Objective

To compare the effect of Dexmedetomidine versus Midazolam for sedation of critically ill patients.

Materials and Methods

A prospective, randomized, double blinded study was undertaken in the Department of Emergency Medicine, of Chigateri General Hospital and Bapuji Hospitals attached to JJM Medical College, Davanagere from March 2012 to March 2013. A total of 100 patients aged above 18 years who were critically ill and admitted to Intensive care units of the above hospitals were included as subjects. An informed bilingual written consent was obtained either from patient if they were conscious and co operative or Immediate Kith and Kins of the patients. The inclusion and exclusion criteria were as follows,

Inclusion Criteria

- Patients aged 18 years and above
- Intubated and mechanically ventilated for less than 96 hours prior to start of study drug.
- Anticipated ventilation and sedation duration of at least 3 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.
- Serious central nervous system pathology.
- 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.

About 100 patients who satisfied the inclusion and exclusion criteria were allocated randomly in to two groups by using random numbers table.

Group I received Dexmedetomidine at a loading dose of 1microgm/kg and maintenance dose of 0.8 mg/kg/hr.

Group II received midazolam at a loading dose of 0.05 mg/kg and a maintenance dose of 0.06 mg/kg/hr.

In the Intensive care unit, after randomizing the selected patients into either of one group, an IV line was accessed. Patients were connected to the monitors to record pulse, O_2 saturation, NIBP and ECG.

Each patient received study drug within 96 hours after intubation. Sedatives used before study enrollment 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 of -2 to +1 at the time of study drug initiation.

Optional blinded loading doses (up to 1 μg/kg dexmedetomidine or 0.05 mg/kg midazolam) could be administered at the investigator's discretion. The starting maintenance infusion dose of blinded study drug was 0.8 μg/kg per hour for dexmedetomidine and 0.06 mg/kg per hour for midazolam, corresponding to the midpoint of the allowable infusion dose range.

Dosing of study drug was adjusted by the managing clinical team based on sedation assessment performed with the RASS a minimum of every 4 hours.

Patients in either group not adequately sedated by study drug titration could receive 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 with a maximum dose of 4 mg in 8 hours.

If oversedation (RASS range, -3 to -5) did not respond to decreasing study drug infusion rate, the infusion was stopped until patients returned to the acceptable sedation range.

A daily arousal assessment was performed throughout the treatment period using RASS range. Safety was assessed by monitoring laboratory test results, vital signs, electrocardiogram findings, physical examination findings, withdrawal related events, and adverse events.

Statistical Analysis

The data was collected by using predesigned proforma. The data was compiled by using the excel sheet. The data was analyzed using Statistical Package for Social Services (SPSS vs 18). The qualitative data was presented by using frequencies and percentages. The quantitative data was analyzed by using students 't' test. The qualitative data was analyzed by using chi-square test. A p value of less than 0.05 is considered as statistically significant and more than 0.05 is considered as not significant.

Results

A prospective, randomized, double blinded study was conducted in order to evaluate the Dexmedetomidine as sedative in comparison with Midazolam. A total number of 100 patients were randomized in to two groups. One group of 50 patients received Dexmedetomidine and another group of 50 patients received Midazolam.

The mean age of the subjects of Dexmedetomidine group was 41.9 (±12.4) years and patients of midazolam group was 41.1 years. There was no statistically significant difference between the age groups. About 26% of the patients in Dexmedetomidine group and 30% of the patients in Midazolam group belonged to 51– 60 years age group. About 30% of the patients in midazolam group also belonged to less than 30 years age group.

About 52% of patients in Dexmedetomidine group and 54% of the patients in Midazolam groups were females. There was no statistically significant difference between the sex and Groups.

The mean weight of the patients in Dexmedetomidine group was 57.2 (± 13.5) kgs and the mean weight of the patients in Midazolam group was 57.8 (±12.2) Kgs. There was no statistically significant difference between the weights of the patients of both the groups (Table 1).

The mean sedation score was 0.6 in dexmedetomidine group and 0.1 in Midazolam group at 5 mins after admission. The mean sedation score was -1.4, -2.0, -1.7 and -1.1 at 10 min, 15 min, 20 min and 25 minutes intervals after admission in Dexmedetomidine group. The mean sedation scores

were -1.0, -1.7, -1.5 and -1.5 at 10 min, 15 min, 20 min and 25 minutes intervals (Table 2).

About 22% of the patients belonging to Dexmedetomidine group and 44% of the patients in Midazolam group required additional sedation. There was statistically significant difference between the Dexmedetomidine and Midazolam groups (Table 3).

Discussion

Sedation helps in allaying the anxiety, increase tolerance and to improve the outcomes of intervention is the Intensive care Unit [1].

The available literature have shown that the sedatives should have rapid onset of action, effective in providing the adequate sedation, should allow the rapid recovery, easy to administer, lack drug accumulation and should have less side effects and interaction with other drugs [6]. Over sedation and under sedation are also substantial including self removal of intraluminal tubes and poor patient–ventilator synchrony [7].

Midazolam is a potent benzodiazepine by including properties including hypnotic, amnestic, anticonvulsant and anxiolytic activities. It is used frequently used medication given for sedation. It has number of beneficial effects including fast onset and limited duration of action. Even after its beneficial effects, the midazolam also have other untoward effects including restlessness, paradoxical reaction, cognitive impairment, amnesia and respiratory depression [11].

Many newer sedatives are available in the market. Dexmedetomidine is one such newer sedative which is α_{2a}adrenoreceptor agonist with a unique mechanism of action providing sedation and anxiolysis via receptors within the locus ceruleus,

Table 1: Socio Demographic Profile of the study population

Socio Demographic profile	Dexmedetomidine n (%)	Midazolam n (%)
Age group		
Less than 30 years	12 (24.0)	15 (30.0)
31 – 40 years	11 (22.0)	7 (14.0)
41 – 50 years	11 (22.0)	11 (22.0)
51 – 60 years	13 (26.0)	15 (30.0)
More than 60 years	3 (6.0)	32(4.0)
Gender		
Male	24 (48.0)	23 (46.0)
Female	26 (52.0)	27 (54.0)
Mean Weight in Kg	57.2 ± 13.5	57.8 ± 12.2

Table 2: Distribution of the study group according to sedation scores at initial hours

Sedation scores at	Group		t value	p value, Sig
	Dexmedetomidine Mean ± SD	Midazolam Mean ± SD		
5 min	0.6 ± 1.9	0.1 ± 1.7	1.359	0.177, NS
10 min	-1.4 ± 2.2	-1.0 ± 1.8	-0.951	0.344, NS
15 min	-2.0 ± 1.6	-1.7 ± 1.7	-1.025	0.308, NS
20 min	-1.7 ± 1.7	- 1.5 ± 1.8	-0.683	0.497, NS
25 min	-1.1 ± 1.7	-1.5 ± 1.7	1.083	0.281, NS

Table 3: Distribution of the study group according to add on sedation

Add on sedation	Group		Total N (%)
	Dexmedetomidine	Midazolam	
Not required	39 (78.0)	28 (56.0)	67 (67.0)
Required	11 (22.0)	22 (44.0)	33 (33.0)
Total	50 (100)	50 (100)	100 (100)

a small nucleus present in the pons, analgesia via receptors in the spinal cord, and attenuation of the stress response with no significant respiratory depression [8]. The lack of respiratory depression, sympatholytic blunting of the stress response, preservation of neutrophil function and may also establish a more natural sleep like state [8].

In the study done by Riker et al Dexmedetomidine had shown that it is effective for long term infusion in the critical care setting for its sedation levels and reduction of over sedation [7].

A study by Riker et al. [8], Herr et al. [12] and Jakob et al. [13] have also found that there was no significant difference between the Dexmedetomidine and Midazolam groups in a group of Mechanically ventilated patients. In a group of eclamptic patients the mean sedation and analgesic scores better in both group of patients [14].

The rates of additional analgesics requirement was much in Midazolam group compared to Dexmedetomidine group. In a similar study by Riker et al. [8], the patients who were on Dexmedetomidine group experienced less adverse effects compared to Midazolam group and needed less number of rescue analgesic [15].

In a study by Herr et al, the rates of receiving the additional drugs were less in Dexmedetomidine group compared to Midazolam group in group of CABG pateints [12].

A study by Mermis et al have also found the anti-inflammatory property of Dexmedetomidine [16].

Conclusion

This study had shown the efficacy of Dexmedetomidine as equal as Midazolam. The hemodynamic parameters also remained normal while use of this drug. This study had also shown that the less adverse effects and number of add on sedative agents were less in Dexmedetomidine group compared to midazolam. However, this study is not without limitations. The sample size was not determined scientifically. Even though this is a randomized controlled the results of this study cannot be generalized. But this study has made an effort to find out some aspects of use of Dexmedetomidine as sedative. Further research with this drug can explore more knowledge.

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