ISSN (Print): 2663-9491 ISSN (Online): 2789-6897

Original Article

Efficacy and Safety of Dexmedetomidine vs Midazolam for Sedation of Critically Ill Patients in Intensive Care Unit: A study in a tertiary care hospital, Dhaka, Bangladesh

DOI: https://dx.doi.org

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Received: 30 OCT 2021
Accepted: 08 OCT 2021
Published: 11 NOV 2021

Published by:
Sheikh Sayera Khatun Medical College Gopalganj, Bangladesh

How to cite this article:
Anwar MM, Momen SHMA, Kabir MA, Hossain M. Efficacy and Safety of Dexmedetomidine vs Midazolam for Sedation of Critically Ill Patients in Intensive Care Unit: A study in a tertiary care hospital, Dhaka, Bangladesh. The Insight [Internet]. 2021 Nov. 12 [cited 2021 Nov. 12];4(01):68-74. Available from: https://bdjournals.org/index.php/insight/article/view/91

ABSTRACT

Introduction: *Sedation with Midazolam in intensive care unit (ICU) has some adverse effects.Dexmedetomidine, an a2 agonist available for ICU sedation may reduce adverse effects and enhance patients' comfort.* ***Objectives:*** *To compare the efficacy and safety betweenDexmedetomidine vs Midazolam for sedation of critically ill patientsin ICU.* ***Methods and Materials:*** *Thiswas a prospective open label randomized trial conducted at ICU in Kurmitola General Hospital, Dhaka, Bangladesh on 60 patients of either sex, age above 18 years requiring mechanical ventilation. The study period extended from January, 2019 to December, 2019.* ***Interventions:*** *Dexmedetomidine {(0.2-0.8ug/kg/hour. (n=30)}andMidazolam {(0.02-0.1 mg/kg/hour (n=30)} titrated to achieve mild to moderatesedation (RASS scores-2 to+1). Sedation was continued as long as clinically indicated.* ***Results:*** *In this study time in target sedation range were 80% in Dexmedetomidine group and 76.67% in Midazolam group (p value=0.756). In Dexmedetomidine group 86.67% patients completing all daily arousal assessment and were 83.33% in Midazolam group (p value=0.718). There was no significant difference between two groups in case of efficacy outcome. In case of safety outcome, the most significant adverse effect of Dexmedetomidine was bradycardia (p value = 0.02) and most significant adverse effect of Midazolam was tachycardia (p value = 0.0001). There was a minimal difference noted in infection and mortality in both the groups.* ***Conclusion:*** *There was no significant difference between Dexmedetomidine and Midazolam in time at targeted sedation level in mechanically ventilated ICU patients. At comparable sedation levels, both Dexmedetomidine and Midazolamtreated patients completing all daily arousal assessment.* The most notable

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adverse effect of Dexmedetomidine was bradycardia and for Midazolam was tachycardia.Indeed, there was a minimal difference noted in both the groups in case of efficacy andsafety outcome forsedation.

Key Words: Dexmedetomidine, Intensive Care Unit (ICU), Midazolam.

The Insight 2021; 4(1): 68:74

INTRODUCTION

Mechanically ventilated patients in intensive care unit (ICU) required sedation and analgesia in order to tolerate the tracheal tube, artificial ventilation and other intensive care procedures such as bronchial suctioning, physiotherapy and catheter placement. Sedation may improve outcome by reducing the stress response and its sequence to those interventions. There is no ideal agent for ICU sedation. An ideal sedative should provide adequate sedation and pain control, rapid onset of action and allow rapid recovery after discontinuation, minimal systematic accumulation and minimal delirium without increasing overall health cost. For decades, Gamma-amino butyric acid (GABA) receptor agonists and benzodiazepines such as Midazolam have been the most commonly administered sedative drugs for ICU patients worldwide[1, 2]. It has a rapid recovery period and a fast onset time for sedative effects. But the half-life of its active metabolite is lengthy. With periodic dosages it results in extended sedation and a sleepy state;[3] also it can result in respiratory depression by diminishing respiratory response to carbon dioxide [4]. So, pharmacological agents with trifling hostile effects should be observed for this purpose. Dexmedetomidine is considered as an alternative to traditional sedation in the ICU. It is known as a highly selective α2-adrenoreceptor agonist with sedative and analgesic effects [4, 5]. Also, it acts at the locus coeruleus and spinal cord to exert anxiolytic as a selective a2-receptor agonist and gives sedative effects without respiratory depression [6, 7]. Moreover, its preferred for its cardiac protective effect against myocardial ischemiahave proved that Dexmedetomidine is well tolerated for respiratory functions even at high plasma dosages. It is a drug, which can be used for its positive effects in conscious sedation. Because of its sympatholytic effects Dexmedetomidine can also result in hypotension and bradycardia [8]. To avoid over sedation many protocols advise daily sedation interruptions to assess the level of sedative in the patient [9]. The major challenges in the ICU management are to assess ICU sedation, over-sedation and under sedation. Suitability of Dexmedetomidine as a sedative in the ICU setting is questioned bearing in mind that most often the critically ill patients may need sedation for weeks at a time. Several sedation scoring scales have been developed for the assessment of sedation level and are used in studies to assess the amount of time a patient spends with in desirable 'target range'. The first standardized procedural measurement for sedation was The Richmond Agitation Sedation Scale (RASS) [10, 11]. Other physiological factors such as heart rate (HR) and Blood pressure also provide objective measures by which sedation level can be assessed [12]. In our study, we intended to compare the effects of Dexmedetomidine vs Midazolam for sedation of critically ill patients in intensive care unit.

METHODOLOGY AND MATERIALS

This prospective, open-label, randomized trial was conducted on a total of 60 patients of either sex, ageabove 18 years, requiring mechanical ventilation in ICU at Kurmitola General Hospital: A Tertiary Care Hospital, Dhaka, Bangladesh. The protocol was approved by the review board of the hospital and all patients or

their representatives provided written informed consent. The study period extended from January, 2019 to December, 2019. The study was divided into two groups, 30 patients who received Midazolam as a sedative agent, whereas included 30 patients who received Dexmedetomidine as a same purpose. Then the efficacy out comes and safety outcomes of both the groups were observed and recorded carefully. The duration of the treatment was six days. During the treatment, the sedation scores were measured with the Richmond Agitation Sedation Scale (RASS). Efficacy outcome measures percentage of time within the target sedation range (RASS score -2 to+1). A daily arousal assessment was performed, during which patients within the RASS range of -2 to+1 were asked to perform 3 tasks (Open eyes to voice command, track investigator with eyes and squeeze hand)[13]. Patients were considered awake when they could perform the above 3 tasks. If patients were over sedated to a RASS value of -3 to-5, study drugs was interrupted until a RASS of -2 to+1 was achieved and then the arousal assessment was performed. Blood pressure and heart rate values were considered to assess the safety outcome. Systolic blood pressure 100-140 mm of Hg and Diastolic blood pressure 60-90 mm of Hg were considered as normal. Heart rate 60-100 beats/min became normal. A greater than 30% change from baseline blood pressure or heart rate considered as adverse event. Interventions for bradycardia, tachycardia and hypertension included titration or interruption of study drugs or administration of medications. Then the association was tested between the groups through z- test with p- value calculator at $p<0.05$ was considered as significant for all tests. The researcher used simple statistical data analysis tools to analyze the data and thus the result of the study came out. The inclusion and exclusion criteria of the participants were as follows:

- **Inclusion Criteria**
- age above18 years
- invasive mechanical ventilation
- clinical need for light to moderate sedation

- **Exclusion Criteria**
- transfer from outside institution
- admission after resuscitation from cardiac arrest
- acute severe neurological disorder

RESULTS

A total of 60 patients were selected during the study period. Comprising the primary analysis study population 30 patients received Dexmedetomidine and 30 patients received Midazolam. Majority (55%) of cases were male and (45%) were female. The age distribution of the studied participants majority (50%) were aged above 60 years, (19.04%) were aged between 51-60, 41-50 were (14.28%), 31-40 were (11.90%) and 18-30 were (7.14%) in Dexmedetomidine group. In Midazolam group majority (55%) were aged above 60 years, 16.66% were of age between 51-60, 41-50 were (11.11%), 31-40 were (11.11%) and 18-30 were (5.55%). The mean percentage of time in target sedation range was estimated to be 80.0% for Dexmedetomidine and 76.67% for Midazolam group (p value = 0.756). 86.67% patients completing all daily arousal assessment in Dexmedetomidine group, while 83.33% patients completing all daily arousal assessment in Midazolam group (p value= 0.718). There was no significant difference in efficacy outcome of patients between two groups. The safety outcomes during treatment of the study participants: In Dexmedetomidine group, Bradycardia were significantly more frequent (66.67%), (p value = 0.02). Bradycardia with intervention were (16.67%), Tachycardia were (33.33%), Tachycardia with intervention were (16.67%), Hypotension were (56.67%), Hypotension with intervention were

(23.33%). Infections were (20.00%) and mortality were (16.67%). In Midazolam group, Bradycardia were (36.67%), Bradycardia with intervention were (10.00%), Tachycardia were significantly more frequent (83.33%),(p value = 0.0001). Tachycardia with intervention were (33.33%), Hypotension were (60.00%), Hypotension with intervention were (23.33%), Infections were (26.67%), and mortality were (20.00%). The sedation scores were observed by RASS ranging from -2 to+1.

Table I: Distribution of the studied participants by sex. (n=60)

Sex	Dexmedetomidine(n=30)	Percentage (%)	Midazolam (n=30)	Percentage (%)
Male	17	56.66	16	53.33
Female	13	43.34	14	46.67

Table II: Distribution of the studied participants by age. (n=60)

Age (in Years)	Dexmedetomidine(n=30)	Percentage (%)	Midazolam (n=30)	Percentage (%)
18-30	2	06.67	02	06.67
31-40	3	10.00	03	10.00
41-50	4	13.33	03	10.00
51-60	6	20.00	05	16.67
>61	15	50.00	17	56.67

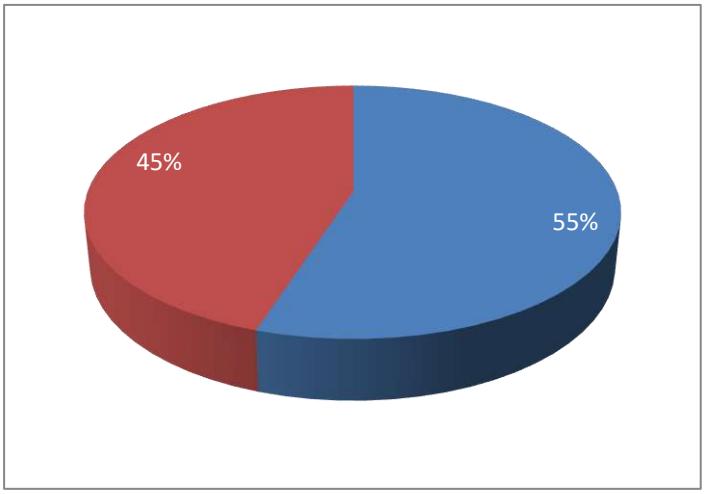

Figure-I: Gender distribution of the participants.(n=60)

Table III: Efficacy outcomes in patients treated with Dexmedetomidine vs Midazolam. (n=60)

Outcome	Dexmedetomidine (n=30)	Percentage (%)	Midazolam (n=30)	Percentage (%)	p value
Time in target sedation range (RASS, Score-2 to+1)	24	80.00	23	76.67	0.756
Patients completing all daily arousal assessments	26	86.67	25	83.33	0.718

Table IV: Safety outcomes during treatment with Dexmedetomidine vs Midazolam. (n=60)

Outcome	Dexmedetomidine (n=30)	Percentage (%)	Midazolam (n=30)	Percentage (%)	p value
Bradycardia	20	66.67	11	36.67	0.02
Bradycardia with intervention	05	16.67	03	10.00	0.447
Tachycardia	10	33.33	25	83.33	0.0001
Tachycardia with intervention	05	16.67	10	60.00	0.136
Hypotension	17	56.67	18	60.00	0.794
Hypotension with intervention	07	23.33	07	23.33	1.0
Infections	06	20.00	08	26.67	0.541
Mortality	05	16.67	06	20.00	0.741

DISCUSSION

In this study, we made a comparison between the efficacy and safety of Dexmedetomidine and Midazolam in ICU sedation. The primary outcome for this investigation, time in the target sedation range was 80.0% in Dexmedetomidine group and 76.67% in Midazolam group. This finding similar with some previous studies, which suggested that Dexmedetomidine attained the sedation target more frequently.[14, 15] In Esmaoglu and colleagues,16 RASS was used to ensure that patients were at an appropriate sedation level, but they did not mention the record of the time length of patients maintained at these target levels (RASS, -2 to+1). Bradycardia and bradycardia with intervention were more frequent in Dexmedetomidine treated patients, while tachycardia were more frequent in Midazolamtreated patients. Richard R. Riker: et al17: in their study showed the similar safety outcome. They found that Dexmedetomidine treated patients developed less tachycardia and most notable adverse effect was bradycardia. Jakob et al. 18 (2012) carried out two studies where the MIDEX trial involved 500 patients that compared Dexmedetomidine with Midazolam. These two studies focused on time at target sedation levelwithout the use of rescue therapy, tolerability to the duration of mechanical ventilation, hemodynamic stability, and post sedation delirium.

Siobal:etal: 19. in 2006, conducted a study using Dexmedetomidine to simplify extubation in ICU patients. They showed that Dexmedetomidine maintains adequate sedation without hemodynamic instability or respiratory drive depression. A total of 24 trials involving 2419 critically ill patients from over 11 countries were identified and subjected to meta-analysis by Tan and Ho20 which showed that significant heterogeneity existed between studies on Dexmedetomidine. Infections developing in ICU patients are associated with increased lengths of stay, cost, and mortality [21]. In this study we noticed average percentage of infections and mortality.

LIMITATIONS OF THE STUDY

This study has several limitations. First there were a small number of patients that include no control. Second, as it was an open-label study, there was a chance of bias and third, delirium was not addressed in this study.

CONCLUSION AND RECOMMENDATIONS

In this study, there was no significant difference between Dexmedetomidine and Midazolam in time at targeted sedation level in mechanically ventilated ICU patients. At comparable sedation levels, both Dexmedetomidine and Midazolam treated patients completing all daily arousal assessment. The most notable adverse effect of Dexmedetomidine was bradycardia and for Midazolam was tachycardia. Indeed, there was a minimal difference noted in both the groups in case of efficacy and safety outcome for sedation.Finally, in the study, we found a very few advantages in safety outcome of Dexmedetomidine compared with the GABA agonist Midazolam. Future studies of ICU sedation must focus on additional important clinical outcomes, including prevalence of delirium and time of mechanical ventilation. The study population was selected from one selected hospital in Dhaka city, so that the result of the study may not reflect the exact picture. Large scale multicenter study should be carried out to verify the study findings.

ACKNOWLEDGMENT

Authors acknowledge Brigadier General Dr. Jamil Ahmed, Director of Kurmitola General Hospital, Dhaka and also wish to acknowledge all the doctors and nursing staff of the Intensive Care Unit (ICU) of this hospital for their cooperation for collecting the patient's data.

CONFLICT OF INTEREST

No conflict of interest.

FUNDING

None

ETHICAL APPROVAL

Ethical approval was taken from the ethical review board of the hospital.

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