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Sedative and hemodynamic response of dexmedetomidine in critically ill South Indian population

Arunkumar Muthalu[1], Arthi Asokan[2], Vimala Ananthy[3]

[1]Assistant Professor, Department of Critical Care Medicine, [3]Associate Professor, Department of Pharmacology, Mahatma Gandhi Medical College and Research Institute, [2]Associate Professor, Department of Anesthesiology, Sri Venkateshwara Medical College and Research Institute, Puducherry, India

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ABSTRACT

Background: Dexmedetomidine is a selective alpha-2-adrenoceptor agonist. It exerts both sedative and analgesic effects through mechanisms different from those of other sedatives. The safety and efficacy of dexmedetomidine are altered by various factors. **Aims and Objectives**: This study aims at identifying the various factors that will affect the sedative and hemodynamic responses of dexmedetomidine in seriously ill patients. **Materials and Methods:** A continuous infusion of dexmedetomidine (0.2–0.7 μg/kg/h) was administered to intensive care unit patients who needed sedation. We investigated the safety and effectiveness of administering dexmedetomidine between responders and non-responders over a short (≤24 h) and lengthy (>24 h) period. **Results:** A total of 84 patients were analyzed who received dexmedetomidine. The longest possible duration of dexmedetomidine administration was 24.7 days and 7.8 days, respectively. Compared to the first 24 h, the number of patients who needed more sedatives or analgesics was not increasing beyond that time. In the first 24 h and after the first 24 h, 35 out of 84 patients (41.2%) and 22 out of 84 patients (26.3%), respectively, needed more sedatives; in the first 24 h and after the first 24 h, 22 out of 84 patients (26.0%) and 18 out of 84 patients (21.4%) needed more analgesics. **Conclusion:** The safety and effectiveness of dexmedetomidine were similar across the demographic factors in this study. The interindividual variability due to pharmacokinetic parameters can be further studied along with pharmacogenomic factors that may cause the difference in the responses to dexmedetomidine use.

Key words: Dexmedetomidine; Sedation; Intensive care; Ramsay sedation scale

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INTRODUCTION

There is growing awareness of the significance of optimizing sedation levels in critical care. Maintaining a targeted "ideal" sedation level based on each patient's condition is a major concern for many critical care specialists to prevent unfavorable outcomes such as respiratory depression, pneumonia, delirium, prolonged mechanical ventilation, psychological issues, and higher treatment costs due to oversedation.[1,2] However, it has proven difficult to optimize sedation levels in intensive care unit (ICU) patients, especially for those who need long-term sedation, sometimes for serious diseases that are hard to manage. While long-term sedation with propofol and midazolam has been prevalent, oversedation and respiratory depression have been considered inevitable side effects. Dexmedetomidine is a selective alpha-2-adrenoceptor agonist. It exerts both sedative and analgesic effects through mechanisms different from those of other sedatives, such as midazolam and propofol, and provides sedation characterized by a prompt response to stimuli with no respiratory depression. It is a selective agonist of alpha-2 adrenoceptors. It produces sleep with a quick reaction to stimuli and no respiratory depression, acting as a sedative and analgesic through distinct processes from those of midazolam and propofol.[3-5]

Address for Correspondence:
Arunkumar Muthalu, Assistant Professor, Department of Critical Care Medicine, Mahatma Gandhi Medical College and Research Institute, Puducherry, India. **Mobile:** +91-9585787226. **E-mail:** arunthemaster@gmail.com

In the ICU, sedation is used to maximize patient comfort and safety while lowering agitation and anxiety to provide the best possible care. Lighter sedation has been prioritized lately, but in the past, the intensive sedation of patients was a standard practice in the ICU with the notion that it would assist patients in accepting mechanical ventilation. An extended stay in the ICU and more time spent on a mechanical ventilator are linked to oversedation. On the other hand, severe patient agitation linked to undersedation may result in longer ICU stays, more time spent on mechanical ventilation, physiological stress, and higher rates of self-extubation. To maximize patient care, a compromise between the two extremes must be established. It was stressed to use a lighter sedation in conjunction with daily sedation awakenings or sedation level measurement. First-line medicines for analgosedation were advised to be opioids, followed by non-benzodiazepines such as propofol and dexmedetomidine. Benzodiazepines have been linked to longer hospital stays, a higher chance of developing ICU-related delirium, and a longer time to be released from the mechanical ventilator when compared to other sedatives. The use of dexmedetomidine has grown over time, but its application in clinical practice is hindered by the fact that not all patients are able to reach their desired level of sedation. According to research, at least 1 out of every 8 patient studies did not show efficacy. Rates of failure in the range of 21–50% have been reported in other trials. Although the exact causes of the great variation in clinical response remain unknown, a number of theories have been put up. This study examines the literature on the function of patient characteristics in patients with severe illnesses and the precise role played by them in altered safety and efficacy.[6-8]

Aims and objectives

This study aims to identify the factors associated with sedative and hemodynamic response of dexmedetomidine in critically ill South Indian population.

MATERIALS AND METHODS

This is an observational study of patients in the critical care unit who were in need of sedation in a tertiary care hospital in south India. The sampling method used was convenient sampling.

Inclusion criterion

Intubated and non-intubated patients admitted to the ICU with the requirement of sedation.

Exclusion criteria

Patients who have recently (within the previous 30 days) started or are currently receiving a2-agonist and a2-agonist medications, patients with severe arrhythmias or atrioventricular block, and diminished left ventricular function. Patients with head injuries, hearing loss, meningitis, encephalitis, facial and ocular trauma, severe hepatic derangement, renal insufficiency necessitating dialysis, and neuromuscular blockade can all be classified as medical conditions.

Patients who accept to provide informed consent and meet the inclusion and exclusion criteria will be added to the study's enrollment list. Every participant will receive an explanation of the study's objectives and specifics. Every person who is willing to take part in the study will be asked to provide written, informed consent. The following details about the patient will be noted: Age, height, gender, body mass index, information about co-morbidities, routine tests, co-medication, and hormonal status. When a patient shows signs of needing dexmedetomidine-induced sedation, the Ramsay Sedation Scale will be used to score the patient's level of sedation. When the patient's RSS is ≤2, a dexmedetomidine infusion will begin, with a dosage of 1.4 mcg. To prevent any side effects from other medications, dexmedetomidine will be administered after the patient has awakened. Before starting the study medication infusion, IV fluid treatment will be used to raise the central venous pressure to 6 mmHg. One hour will be the desired infusion time, and the targeted infusion rate will be 1.4 mcg/kg/h. A lower infusion rate of dexmedetomidine will be administered if the patient's systolic arterial pressure drops below 90 mmHg. Throughout the study period, heart rate (HR), systolic and diastolic blood pressure (DBP), and RSS scores will be measured every 5 min (1 h after the initial dose). Patient responses to dexmedetomidine will be used to categorize them into responders and non-responders.

Responders

Effective sedation with a score of >3 with the Ramsay sedation score.

Non-responders

With a Ramsay sedation score of <3, the addition of a new continuous infusion sedative at any dose or the resumption of a previously stopped sedative when dexmedetomidine was being administered at an infusion rate of 0.7 mcg/kg/h or above were considered inefficient uses of dexmedetomidine.

Safety evaluation

The following is how the protocol describes the incidence rates of bradycardia, hypertension, and hypotension associated with treatment: Systolic blood pressure (SBP) <60 mmHg, DBP <40 mmHg, or a decrease in SBP of ≥50% from the baseline, requiring infusion or raising the dose of vasopressors or fluid infusion ≥500 mL within an h; hypertension is defined as SBP >180 mmHg, DBP

>100 mmHg, or an increase in SBP of ≥50% from the baseline, requiring infusion or raising the dose of antihypertensive agents; and bradycardia is defined as HR <40 bpm or a decrease in SBP of ≥50% from the baseline, necessitating infusion or raising the dose of positive chronotropic medications or the use of a pacemaker. Treatment-associated adverse events were defined as any adverse events that were not deemed to be "not related" to dexmedetomidine. Secondary safety assessments included adverse events, withdrawal assessments of the incidence rates of adverse events associated with withdrawal symptoms (e.g., tachycardia, elevated blood pressure, nausea/vomiting, headache, tremors, anxiety, sweating, or agitation), and rebound assessments of the power source post-infusion modifications to mean arterial blood pressure (MBP), HR, and rate-pressure product (RPP). If hematology or blood chemistry revealed clinically significant aberrant results, adverse events were to be documented. Similar to the primary endpoint, all adverse events deemed "not related" to dexmedetomidine have been included in the definition of treatment-related adverse events.

Statistical methods

The sample size determined the lowest number of treatment-related hypotension, hypertension, or bradycardia cases that could be identified. Assuming that bradycardia has the lowest incidence of all those events at 5%, 59 people would be required to detect at least one incident of 5% treatment-related adverse events with 95% likelihood. Eighty patients were estimated to be in the sample, which represents 20% of the cases of dropout. Furthermore, enrollment of approximately 15% of patients in the medical ICU was planned.

By dividing the total number of treatment-related adverse events –including protocol-defined hypotension, hypertension, and bradycardia – by the total number of treatment days for all patients, including the 24-h observation period, the incidence rates per person per day of these events were determined. Using the Sumi and Tango methods of the score test, the incidence rates during the first and second 24 h were compared with each other. The rates of occurrence of the other treatment-related adverse events were examined in the secondary analysis using the same methodology as the original study. The other evaluations made use of descriptive statistics. All of the patients who got treatment with dexmedetomidine made up the whole analysis set of patients used in the analysis. For all statistical analyses, the significance level was fixed at $\alpha = 0.05$ (two-tailed).

RESULTS

Patient demographics

A total of 84 patients were analyzed who received dexmedetomidine. Out of 84 patients, 52 (61.9%) were surgical ICU patients and 34 (38.1%) were medical ICU patients, respectively (Table 1). Compared to surgical ICU patients, medical ICU patients needed more time under anesthesia. For both the surgical and medical ICU patients, the longest possible duration of dexmedetomidine administration was 24.7 days and 7.8 days, respectively (Table 2). Dexmedetomidine was administered to 69 patients (82.1%) both before and following extubation. Due to bradycardia or bleeding after surgery, two of the fifty-two surgical ICU patients stopped receiving dexmedetomidine infusions throughout the first 24 h.

Safety

Between the first 24 h and the following 24 h, there were no variations in the incidence of treatment-related hypotension, hypertension, or bradycardia as specified by the protocol, expressed as per person per day. In addition, there were no variations in those values across the patients in the medical and surgical ICUs (Table 3).

Table 1: Demographic details of patients receiving dexmedetomidine in critically ill patients

Demographic factors	Surgical ICU, n (%)	Medical ICU, n (%)	Total, n (%)
	54 (61.9)	30 (38.1)	84 (100)
Age (years)			
Mean±SD	64.1±10.3	65.9±11.9	64.9±11.8
Sex			
Male	29 (34.5)	20 (23.8)	49 (58.3)
Female	26 (30.9)	10 (11.9)	36 (42.8)
Body weight (kg)			
Mean±SD	61.2±9.3	55.30±9.76	57.66±10.19
Specific medical disease			
Respiratory disease	9 (10.7)	10 (11.9)	19 (22.6)
Cardiac disease	11 (13.1)	7 (8.3)	18 (21.4)
Vascular disease	3 (3.5)	4 (4.7)	7 (8.3)
Other	4 (4.7)	4 (4.7)	8 (9.5)

ICU: Intensive care unit

Table 2: The average duration of treatment with dexmedetomidine

Parameter (days)	Surgical ICU	Medical ICU
Mean±SD	5.8±3.3	6.4±3.5

ICU: Intensive care unit

Table 3: No of adverse event during the administration of dexmedetomidine

Adverse event	Number of adverse events within 24 h	Number of adverse events after 24 h
Protocol-defined hypertension		
Total	20	33
Surgical ICU	8	15
Medical ICU	12	18
Protocol-defined bradycardia		
Total	29	17
Surgical ICU	16	11
Medical ICU	13	8
Protocol-defined hypotension		
Total	12	9
Surgical ICU	3	4
Medical ICU	9	5

ICU: Intensive care unit

Table 4: Number of patients who required additional sedatives

Agent	n (%) within 24 h (n=84)	n (%) after 24 h (n=84)
Additional sedatives	12 (14.2)	24
Propofol	3 (3.5)	12 (14.2)
Fentanyl	5 (5.9)	4 (4.7)
Haloperidol	4 (4.7)	8 (9.5)

When presented as a daily incidence rate per person, the overall incidence rate of treatment-related adverse events that happened within 24 h was much higher than what happened after 24 h. With the exception of elevated blood pressure, which was more common within 24 h than later, there were no variations in the incidence of any adverse event associated with the treatment between the 24-h period and the following. There was no respiratory depression brought on by the treatment. Out of 84 patients, delirium affected 8 (9.5%). Six days following the onset of symptoms, the patient recovered, and one of three incidents was determined to be most likely unrelated to dexmedetomidine. Two other incidents were found to be unrelated to dexmedetomidine, and the patients recovered roughly 5 h and 9 days, respectively, following the start of symptoms. Following the conclusion of the dexmedetomidine infusion, seven patients had passed away from sepsis, multiorgan failure, pneumonia aspiration, respiratory failure, or cardiac failure. No further significant adverse events were detected in relation to the infusion of dexmedetomidine, and these events were not considered to be related to the infusion.

16 out of 84 patients experienced a total of 33 adverse reactions associated with withdrawal symptoms; all of these events, with the exception of one moderate headache event, were minor. There were one instance of elevated blood pressure and one instance of moderate headache that were both thought to be related to the medication. MBP, HR, and RPP all slightly rose after the long-term dexmedetomidine infusion was stopped. There were no changes in response to the lengthening of the dexmedetomidine infusion.

Efficacy

With the exception of 7–9 days, 84% of the patients were within the desired sedation range (RASS < 0) while receiving the study medication. When two patients with daytime arousal (RASS >0) and a medical ICU patient with significant agitation (including aggressive actions and tube tugging) were examined on days 7–9, the ratio of duration in the desired sedation range dropped to about 71–76%.

Compared to the first 24 h, the number of patients who needed more sedatives or analgesics was not increasing beyond that time. In the first 24 h and after the first 24 h, 35 out of 84 patients (41.2%) and 22 out of 84 patients (26.3%), respectively, needed more sedatives; in the first 24 h and after the first 24 h, 22 out of 84 patients (26.0%) and 18 out of 84 patients (21.4%) needed more analgesics (Table 4).

After being administered for 24 h, there was no increase in the dosage of additional sedatives or analgesics. Many patients also received midazolam and propofol as supplementary sedatives. Some patients received fentanyl or haloperidol for sedation, despite the fact that neither substance is a sedative. For analgesia, pentazocine, buprenorphine, fentanyl, or other analgesics were used.

DISCUSSION

This study set out to assess the long-term safety and effectiveness of dexmedetomidine. We contrasted the safety and effectiveness of dexmedetomidine in the first 24 h versus the second 24 h. This prospective study's design and methodology were distinct.

Dexmedetomidine, compared to other sedatives, does not cause respiratory depression or can be given continuously both during and after intubation. A light to moderate level of sedation is provided by dexmedetomidine, which has the special quality of being arousable. Because of their tendency to generate deeper sedation and their ability to cause respiratory depression, propofol and midazolam are generally not administered following

extubation. As a result, it was determined not to compare the two. Ethical concerns prevented the use of a placebo as a comparative.

In comparison to patients who just need short-term sedation, patients who need long-term sedation are usually in more severe conditions, and they occasionally require deep sedation. Other sedatives may be administered in addition to or instead of dexmedetomidine when deep sedation is necessary in a typical ICU situation. As a result, the concurrent use of additional sedatives in the typical ICU context was permitted in this investigation. In this study, a long-term investigation based on its application in a typical ICU setting was deemed to be more significant.[9,10]

Both surgical and medical ICU patients tolerated long-term infusions of dexmedetomidine well. The study's findings demonstrated that, as compared to the first 24 h of therapy, there was no rise in treatment-related hypotension, hypertension, bradycardia, or other adverse effects over the course of a long administration period. After the dexmedetomidine was stopped, MBP, HR, and RPP slightly rose, but these changes were not related to the lengthening of the dexmedetomidine infusion. After the long-term treatment of an α2-receptor agonist was stopped, there was concern about a withdrawal syndrome or rebound effect, but there was no evidence of either. In line with other research, there was no need to reduce the dosage of dexmedetomidine.[11] After 24 h, there was no decline in the ratio of the duration to the total duration of the dexmedetomidine infusion. Moreover, there was no sustained rise in the quantity or number of patients requiring additional sedatives or analgesics over time.

To quickly raise the plasma concentration of dexmedetomidine, a loading dosage must be infused; however, this may have unfavorable side effects such as hypertension.[12] No patient had received a loading dose, despite the fact that loading infusion remained an option for this trial and could be chosen at the investigator's discretion. As soon as the anesthetic's residual effects were noticed following surgery, study medication administration was started in the surgical ICU patients. Research medication was started to be administered to medical ICU patients when other sedatives continued to have a sufficient impact. Dexmedetomidine was either given concurrently with other sedatives or substituted for the other sedatives when the patients were sedated. Thus, there was no need for a loading dose.

This study comprised two patients on non-invasive positive pressure ventilation (NPPV) in a medical ICU. Sedation using dexmedetomidine is recommended in these individuals, as those receiving NPPV must remain conscious to avoid the possibility of aspiration pneumonia from not having airway protection. However, using a face mask during NPPV causes discomfort for these patients and may even cause them to become agitated.[13] In the current investigation, individuals receiving NPPV had sufficient sedation from dexmedetomidine without exhibiting any signs of respiratory depression.

The efficacy and safety evaluations covered both the intubation and post-extubation periods, even though the post-extubation phase was not the primary focus of this study as there was no separate sub-analysis information for the post-extubation period solely. Following extubation, 62 of the 84 patients were given dexmedetomidine. Following their extubation, these patients responded well to long-term dexmedetomidine treatment and no side events suggestive of respiratory depression were noted.

Dexmedetomidine has been shown in multiple prior studies to lower the incidence of delirium. Six out of 84 patients (7.3%) in this trial experienced delirium; one of these cases was determined to be probably unrelated to dexmedetomidine, while the other six cases were not.[14] Nevertheless, this was not a comparison trial, and the ICU did not assess delirium using the Confusion Assessment Method. As a result, we are unable to discuss how dexmedetomidine affects delirium.[15]

Poor patient outcomes and higher treatment expenses are caused by oversedation.[16] As a result, it is preferable to keep the patient's level of sedation just right and avoid oversedation. Furthermore, each patient requires a different amount of sedation because the conditions of patients in ICUs vary greatly. In this trial, light to moderate sedation was achieved by the scientists using dexmedetomidine as a fundamental sedative. When deep sedation was required or when managing sedation with dexmedetomidine alone proved to be challenging, additional sedatives were given concurrently. Consequently, further sedatives were administered to 61.6% and 38.4% of patients, respectively.

Consecutive use of different sedatives with dexmedetomidine offers advantages in long-term use as it makes use of each sedative's quality as needed, even though the interaction between the two needs to be closely controlled. Other sedatives such as midazolam and propofol are frequently used for prolonged ICU sedation. The vasodilatory impact of midazolam is lower than that of propofol or dexmedetomidine. Long-term midazolam usage, however, produces an active metabolite and exhibits significant interindividual variation in pharmacokinetics, leading to a lengthy recovery period to awareness following long-term medication.[17,18]

A patient might additionally develop tolerance with long-term midazolam treatment. Propofol has a quick offset to consciousness and a brief elimination half-life when used long term. On the other hand, long-term propofol administration is linked to a higher risk of infection through the same route, an increased risk of blood lipid accumulation due to the lipid emulsion formulation, tolerance development, and propofol infusion syndrome.[19,20] Dexmedetomidine may have benefits for long-term usage, such as its arousability and lack of correlation with respiratory depression, which can ease extubation and weaning. In addition, as a prolonged ICU stay raises the likelihood of delirium, dexmedetomidine may help lower that incidence. The majority of patients were kept at the desired sedation levels without any dose increases, and the concurrent usage of other sedatives or analgesics did not rise with time, indicating that tolerance did not develop.[21-24] Dexmedetomidine may have a drawback in that individuals with bradycardia or hypotension should use it with extreme caution.

Limitations of the study

The limitations of the study is the less number of sample size.Modifications to the settings of the mechanical ventilator that can affect hemodynamic parameters—like raising the positive end-expiratory pressure, for example—were not assessed. Moreover, dexmedetomidine dose increases occurred too quickly in some patients, which may have added to the general elevated levels of hypotension seen. Lastly, although our facility follows a dexmedetomidine dosage guideline which can differ in different centres.

CONCLUSION

In addition to preserving a patient's typical sleep pattern and causing cooperative sedation that makes them easily arousable, dexmedetomidine also has the effect of sparing opioids and decreases cognitive damage. Regularly performing proper assessments for sedative and delirium together with daily arousal can reduce the amount of time patients spend on ventilatory care, lengthen their stay in the intensive care unit, and enhance the duration and quality of delirium with improved sedation. An effective sedative that is tailored for intensive care units is dexmedetomidine.

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Authors Contribution:
AM- Definition of intellectual content, literature survey, prepared first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation and submission of article; **AA-** Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision; **VA-** Design of study, statistical analysis, and interpretation

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Mahatma Gandhi Medical College and Research Institute, Puducherry, India

Orcid ID:
Arunkumar Muthalu- https://orcid.org/0009-0009-9799-0947
Vimala Ananthy- https://orcid.org/0000-0002-5124-9821

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